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THE MECHANISM OF THE REDUCTION OF RED CELLS AND HEMOGLOBIN FOLLOWING OPERATION FOR TETRALOGY OF FALLOT

HUGH W. JOSEPHS,

From the Department of Pediatrics, Johns Hopkins University Medical School and Hospital

Received for publication July 20, 1949

As is well known, the cyanosis of congenital heart disease is accompanied by an increase in red cells and hemoglobin. Relief of the condition by operation is accompanied by a relatively rapid fall of red cells and hemoglobin until a figure is reached that is normal or at least consistent with what anoxia may persist. The sequence of occurrences is not dissimilar to that present in the newborn period, so that it was of interest to learn whether the mechanism of the blood changes is similar especially in regard to the relation between blood destruction as measured by the urobilin excretion in the stools and blood formation as measured by reticulocyte counts.

PLAN OF STUDY AND METHODS

The plan was to determine the daily urobilin excretion, before and after operation and the variations in reticulocyte counts and compare these with the fall in red cells and hemoglobin percentage. The patients studied comprise a group of cases of "Tetralogy of Fallot" operated upon over a two month period, taken as they came with no attempt at selection except the rejection of those that were too sick for the study. The stool collections were made in a routine manner and urobilin determined on pooled specimens over a period of several days, by the zinc acetate method of Elman and McMaster (1) as modified by the author (2). In this method, stool emulsions were extracted with acid alcohol over night, a fluorescent filtrate prepared with fresh alcoholic zinc acetate and diluted until the fluorescence matched that of a similarly treated solution of purified urobilin diluted 1–2,000,000, using a box specially made for comparing fluorescence. In order to avoid repeated preparation of urobilin, acriflavine was ordinarily substituted in a dilution that matched that of the urobilin standard, the diluted acriflavine solution being made up fresh from a stock solution which was compared with the standard urobilin every few months to be certain that there was no deterioration.

The reticulocytes were determined in a wet preparation made by inverting a cover slip with a small drop of fresh blood over a slide previously smeared with cresyl blue and dried. The determinations of arterial oxygen capacity and content were part of the routine diagnostic study of these patients and were as such copied from the record.

E.E.G.

EEG

TABLE I

NAME	AGE	WT.	DATE OF OPERATION	DATE	R.B.C.	HGB	HEMATOCRIT	RETICULOCYTES	OXYGEN CAPACITY	OXYGEN SATURATION	UROBILIN EXCRETION			
											Period	Average daily excretion	Normal	Index
		kg.						%				*mg.*		*units*
R. B.	17	60	11/12	11/11	8.4	21.5	88	1.6	27.3	30	11/15–17	810	120	6.7
				11/16	6.7	18.1		1.1			11/17–19	1000		8.3
				11/22	6.1	16	50.5	.7	21.5	71	11/22–24	330		2.7
R. M.	15	61	11/11	11/10	7.4	19.5	60.2		27	76				
				11/13	6.2	17		1.2						
				11/16	6.1	16.4		.5			11/15–17	315	122	2.6
				11/19	6.0	17.0					11/17–20	75		.6
				11/22	6.4	17.0			21.5	71				
A. C.	15	50	12/10								12/ 2–4	360	100	3.6
				12/8	9.4	20.1	80	2.0			12/ 4–8	320		3.2
				12/12	6.7	19.0		1.0						
				12/16	5.5	16.5	67	0						
				12/20				0	26	78				
W. B.	13	45	10/12	9/16	8.8	24	78		31.0	19.8	9/14–17	310	90	3.4
											9/20–22	500		5.5
				10/11		23.4								
				10/13	6.4	19.7					10/13–15	175		1.9
				10/16		19.5					10/15–17	140		1.5
				10/23	6.1	18.7					10/22–25	60		.7
				10/27		17			24.8	65.1	10/25–28	53		.6

R. E.	12	35	11/7	11/6	8.6	24	75	.8	28.8	60	11/ 4–6	190	70	2.7
				11/9	8.2	24		.5						
				11/12	8.0	20.5		.2						
				11/16	8.3	18		.6	24.1	85				
O'C	12	50	11/6	10/30	10.7	21.4	78	1.3	30.4	64				
				11/8	8.2	21.4					11/ 6–9	840	100	8.4
				11/11	7.8	20.1		0						
				11/14	7.8	19.4		0	26.8	72				
P. L.	10	52	11/20	11/19	9.2	20	76	1.5	30.0	71				
				11/23	10.2	18		1.2			11/19–25	400	104	3.9
				11/27				0.4			11/25–28	1040		10.0
				11/29				0.1			11/28 to 12/1	450		4.3
				12/5	8.0	17	62	0	27	64	12/ 2–5	150		1.4
J. C.	10	35	12/2	12/1	6.9	17.5	49	1.2	23	63	12/ 1–2	400	70	5.7
				12/4	6.2	14.5		1.0			12/ 3–7	650		9.3
				12/7	4.8	14	49	.8			12/ 7–10	105		3.0
				12/12				.3	21	70				
J. R.	9	20	10/29	10/26	7.5	22	75		33.2	62	10/25–27	395	40	6.9
											10/28–31	295		7.4
				11/1	6.1	19					10/31 to 11/3	320		8.0
				11/5	6.5	18		.2			11/ 3–5	95		1.1
				11/8				0			11/ 5–9	80		2.9
				11/12	6.7	17.8		.5	27.7	70	11/ 9–12	100		2.5
S. M.	8	35	11/27	11/26	9.1	19.5	66	1.4						
				11/29	7.9	19.0		1.5			11/26–12/2	300	70	4.3
				12/5	7.0	16.9	60	1.2			12/ 4–8	270		3.9
				12/9				1.0						

TABLE I—*Continued*

NAME	AGE	WT.	DATE OF OPERATION	DATE	R.B.C.	HGB	HEMATOCRIT	RETICULOCYTES	OXYGEN CAPACITY	OXYGEN SATURATION	UROBILIN EXCRETION			
											Period	Average daily excretion	Normal	Index
		kg.						%				*mg.*		*units*
J. G.	7	18	11/30	11/29	10.0	21.3	81	1.2	29.0	27				
				12/2	7.5	15.4		1.0			11/29 to 12/4	128	36	3.6
				12/6	6.7	16.5	68	1.3			12/ 4–8	60		1.7
				12/14	6.5	16.0	64	.2	24	70	12/ 8–11	38		1.1
S. C.	6	20	12/3	12/2	7.3	19.2	64		25	33				
				12/5	5.9	14.7		2.0			12/ 2–7	320	40	8.0
				12/9	5.7	14.4		1.8			12/ 7–9	162		4.1
				12/12	5.5	14.1	37	.4	20.4	76	12/11–12	40		1.0
H. T.	6	19	11/23	11/21	8.0	24.6	73		29	56				
											11/22–26	280	38	7.4
				11/27				0.1			11/26–28	340		9.0
				12/1				.2			11/28 to 12/1	260		6.8
				12/6	6.8	17.5	68	0	24	88				
C. S.	6	16	10/26	10/25	7.9	18.8	71		28.1	24				
				10/29	6.3	16.6					10/26–30	320	32	10.0
				11/2	6.4	16.5					10/31 to 11/3	173		5.4
				11/5		13			18.8	89	11/ 3–5	44		1.4
J. L.	4	18	11/8	11/7	9.2	21.0	71	1.5	29.5	56				
				11/11	7.2	19					11/ 8–11	280	36	7.7
				11/14				0.5			11/11–13	360		10.0
				11/16	5.9	16.5	51	0.2			11/14–17	150		4.2
				11/21	5.3	15	50		20.5	85	11/17–21	60		1.7

E. M.	3½	15	12/12	12/9	7.9	16.5	76	1.0	23	33	12/ 8–9	150	33	4.5
				12/14	5.9	14.0		2.5			12/11–16	150		4.5
				12/17	6.1	12.6		1.0			12/17–21	115		3.5
				12/20			58	0.7	16.6	75				
J. P.	3	15	11/1	10/30	7.1	21.5	65		25.4	69				
				11/7	6.5	18.5	55							
				11/10	6.3	17					11/ 8–11	14	35	.40
				11/14	6.3	18	49				11/12–14	35		1.0
				11/16					22.2	81	11/14–16	40		1.1
H. F.	2½	11	11/5	10/25	6.6	13.8	62		21.9	15.4	10/25–27	75	30	2.5
				11/4		15					11/ 3– 5	60	30	2
				11/8		12	49				11/ 6– 9	187		6.2
											11/10–12	100		3.3
				11/15		14			18.9	67	11/12–16	30		1.0
C. J.	2	13	11/21	11/20	9.2	17	67		21.5	40				
				11/22				2.3			11/20–25	120	33	3.7
				11/27				0.8			11/25–28	210		6.3
				12/3		13.5		1.0	18.1	67	11/30 to 12/3	40		1.2
C. P.	1½	12	11/9	11/8	5.6	18			25	17				
											11/ 8–12	120	30	4.0
				11/13				2.5			11/12–14	64		2.1
				11/16				.5			11/14–17	16		.53
				11/20	4.7	13.5	39	0.3	20	76	11/17–20	24		.8

RESULTS

The results are summarized in Table I. In order to facilitate the comparison of the urobilin figures, use has been made of an index of urobilin excretion which is to be understood as the ratio between the actual daily excretion and the excretion that is considered the probable normal for the patient's age and weight. It had been found previously that there was a fairly constant ratio between daily uro-

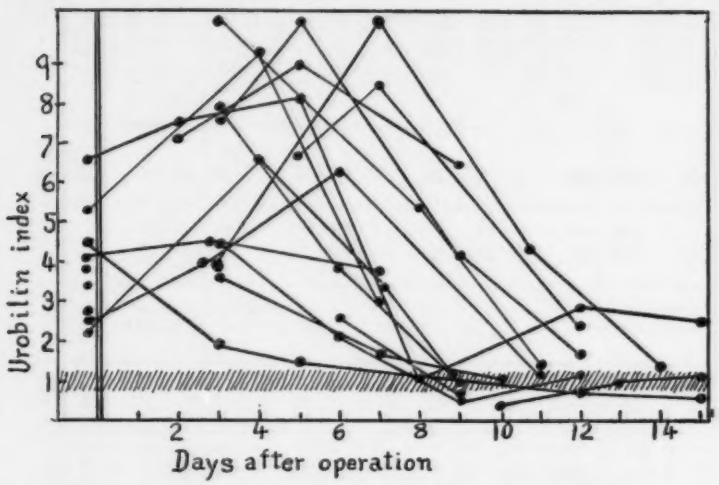

CHART 1. UROBILIN EXCRETION BEFORE AND AFTER OPERATION

bilin excretion and the probable total mass of hemoglobin calculated from the blood volume and hemoglobin concentration (2). Since the child's weight was used to calculate probable blood volume, it is evident that normally there is a fairly constant ratio between weight and urobilin excretion. It is not suggested that the normal excretion in these cases can be calculated by this means, but only that the probable excretion of a normal child of the same age and weight can be so calculated.

These indices have been plotted in Chart 1 in order to provide an easily visualized summary. Three things may be noted. 1) Previous to operation, the urobilin excretion tends to be above the normal level

represented by an index of 1 and on the chart by the shaded zone near the bottom. 2) In the majority of cases for which the figures are sufficient, there occurred a rise within the first week. This rise was in many cases extremely high, even as high as one might expect in a severe hemolytic anemia. Since previous to operation there were few cases with figures above 6, it is probable that any figure above that point following operation was the result of a rise following the operation. 3) Following the rise and sometimes without it there was a fall to lower values, in the great majority to normal levels or approaching normal levels. This fall was generally completed by the

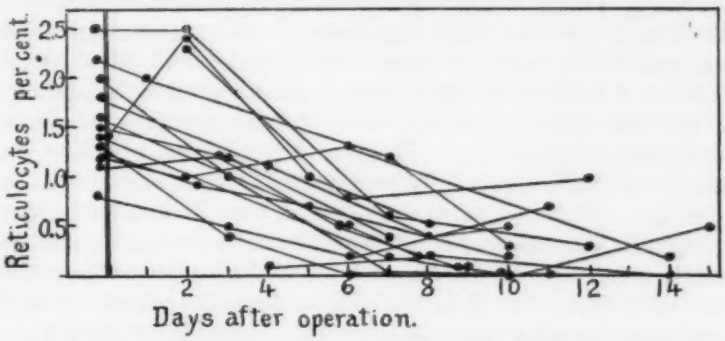

CHART 2. RETICULOCYTE PERCENTAGE BEFORE AND AFTER OPERATION

end of the second week. In some cases the fall extended below the normal level with subsequent rise. There is always some and often considerable lag between the destruction of blood and final excretion of urobilin derived from it. This would mean that the blood destruction on which the urobilin excretion in these cases depends was largely completed within a shorter period than represented in the chart.

The fall in red cells and hemoglobin was relatively rapid at first, as much as 4–5 gms. of hemoglobin in the first two or three days after operation, but thereafter relatively slow so that after two weeks the normal level had not been reached in many instances. This was especially true of the red cells. In a few instances the fall extended below the normal level.

The reticulocytes were in practically all instances above the normal

level previous to operation (Chart 2). After operation the reticulocyte levels fell, gradually reaching points well below normal in the majority of instances by the end of the first week and often continuing to the zero point. The fall was in general linear, but in a few cases there occurred an initial rise followed by a more rapid fall; in only one case did the reticulocytes tend to remain elevated throughout the period of observation, and in two others the fall was delayed.

DISCUSSION

The moderate but definite increase in reticulocyte counts before operation indicates clearly a rise in the rate of blood formation. This is no more than one would expect to be present in anoxemia. The decrease after operation indicates a marked diminution of blood formation, most probably as part of a mechanism by which the numbers of red cells are diminished. As a result of recent studies, it is believed that reticulocytes "mature"—i.e., lose their reticular substance—in about 6 days after appearing in the peripheral blood, and during this time are resistant to destruction (3, 4). It may be seen from Chart 2 that the disappearance of the reticulocytes in general corresponds within a few days with the above period of maturation. From this we may conclude that diminution of blood formation occurs in general soon after operation, although in individual cases there was evident variation. How long the slowing down of hemopoiesis lasts we do not know; there was little if any tendency for reappearance of reticulocytes during the period of observation. The disappearance was independent of such things as the rate and extent of fall in red cells, and the rise in urobilin excretion.

The significance of the urobilin excretion is not so easily settled. As a result of observations over the past twenty years, three things are clear: 1) that urobilin is exclusively derived from the breakdown of hemoglobin, 2) that its excretion is normally related to the total mass of hemoglobin, 3) that variations in its excretion may be used as a measure of variations in the rate of blood destruction. The difficulty in the interpretation arises from the fact that if the total mass of red cells is increased, we would expect a corresponding rise in urobilin excretion, and we have no certain information concerning

the total red cell mass in tetralogy cases.[1] We may, however, use an indirect means of getting a rough but probably adequate solution of the problem.

The possibility that the red cell mass is increased three–four times to correspond to the preoperative urobilin excretion seems at first sight to be borne out by the hematocrit values. If plasma volume remains constant, a hematocrit value of 75 would mean roughly a tripling of the cell mass, one of 80, a quadrupling and so on. There are, however, certain considerations that make it unlikely that the cell mass is increased to any such extent. In the first place, an increase in cell mass to four times its normal value with no change in plasma volume would mean that blood volume would be increased two and a half times. Though there is reason to believe that there is some increase in blood volume, an increase of this extent appears unlikely. In the second place, a calculation of the total urobilin excretion in the postoperative period does not support the possibility of a great increase in red cell mass. The considerations leading to this conclusion will next be taken up.

The fall in hematocrit values following operation indicates an almost unbelievable reduction in red cell mass. For instance, a fall from 75 to 67 would mean a reduction of from three to two times the normal mass, so that a fall of no more than this would account for the loss of cells corresponding to all the red cells in a normal child

[1] There are three articles dealing with blood volume in cyanotic congenital cardiac disease (5, 6, 7). In all three only plasma volume was determined, and from this and hematocrit values, total blood volume and cell mass were calculated. Two of these are in accord in showing a tendency to reduction in plasma volume. The third concluded that plasma volume was increased. Because of the discrepancies which cannot be explained by a reading of the articles, and because in some cases the calculated increases in blood volume and cell volume were so large as to be almost unbelievable, it has seemed best to the author to present his results independently of this published work. It may be that the methods used and the calculations are not applicable in the tetralogy cases. A recent paper by Gibson and others (8) compares the value for cell mass determined with radioactive iron and calculated from plasma volume and hematocrit. He finds as have others that the cell volume is regularly higher when calculated from plasma volume and hematocrit. He ascribes this to the greater concentration of cells in the blood used for hematocrit determinations, a factor that could easily be exaggerated in the cases under discussion in which venous blood was used.

of the same weight. Most of the cell mass reductions calculated in this manner fall well above this figure, in many cases amounting to 3 or even 4 times the total cell mass in a normal individual. There are two ways in which this reduction in cell mass can be effected: (1) Loss of blood at the operation, (2) Destruction of blood in the postoperative period.

The amount lost at operation is not accurately known. On the other hand, if it was thought that the loss was excessive, blood was replaced by transfusion and probably the amount replaced was not so very different from the amount lost. This is admittedly only a guess, but an error on our guess of as much as 200 cc. would account for only about 10 per cent of the total blood volume in the majority of cases.

The remaining 90 per cent of the reduction of cell mass must then be accounted for by post-operative blood destruction and the products of this destruction would appear eventually as urobilin excretion in the stools. Since the normal daily excretion of urobilin corresponds to about one one-hundred-twentieth of the blood in the body (normal life of the red cell—120 days), it is easy to see that the above destruction should give about 120–360 times the normal daily urobilin excretion or a corresponding number of units of urobilin index. Now we have the information on which to base a determination of the total index units in about 12 cases. The figures varied from about 40 to 68 (see Table II). Thus it may be seen that in no case did the urobilin excretion support the hypothesis that the total red cell mass was greatly increased.[2] Since the urobilin excretion before operation amounted to from two to six times the normal we may conclude that the rate of destruction before operation is greater than can be accounted for by increase in hemoglobin mass. In other words, there is a specific destruction of cells or a shortening of their life span. The significance of this will be discussed later.

[2] These calculations are made on the basis of mere reduction of blood volume as indicated by the hematocrit without considering the fall in hemoglobin level. Including the fall in hemoglobin would only serve to magnify the discrepancy between calculated and observed values. The fall in hemoglobin would also be influenced by any excessive loss of blood unreplaced by transfusion. Although some fall in hemoglobin took place in the first few days after operation, in none of the cases studied was this fall to be considered excessive.

TABLE II

Calculation of Units of Urobilin Corresponding to Each Gram Per Cent Fall in Hemoglobin

	UROBILIN INDEX	DAYS (COLLECTED)	UROBILIN		TOTAL FALL IN HGB	UROBILIN OUTPUT PER GM. % FALL IN HGB	HEMATOCRIT
			Units for period	Total units			
					gms. per 100 cc.		
R. B.	(5)	3	(15)				88
	6.7	2	13.5				
	8.3	2	16.5				
	(5.5)	3	16.5				
	2.7	2	5.5	67	6	11.3	50.5
P. L.	3.9	6	23				76
	10.0	3	30				
	4.3	3	13	66	5.5	12	62
J. C.	5.7	1	5.7				49
	9.3	5	46				
	3.0	3	9	61	3.5	17.5	49
J. R.	7.4	3	22				75
	8.0	3	24				
	1.1	2	2	48	5	9.6	
J. G.	3.6	5	18				81
	1.7	4	7				
	1.1	3	3	28	5	5.6	64
S. C.	8.0	5	40				64
	4.1	2	8				
	(2.5)	2	5	53	5	10.6	37
H. T.	7.4	4	29.5				73
	9	2	18				
	6.8	3	20.5	68	7	9.7	68
C. S.	10	4	40				71
	(7.6)	1	7.6				
	5.4	3	16.2	64	6	10.7	
J. L.	7.7	3	23				71
	10.0	2	20				
	6	1	6				
	4.2	3	12.5	61.5	6	10.2	50

TABLE II—*Continued*

	UROBILIN INDEX	DAYS (COLLECTED)	UROBILIN		TOTAL FALL IN HGB	UROBILIN OUTPUT PER GM. % FALL IN HGB	HEMATOCRIT
			Units for period	Total units			
					gms. per 100 cc.		
E. M.	4.5	5	22.5				76
	(4.0)	1	4				
	3.5	4	14	40.5	4	10.1	58
H. F.	(6)	1	6				62
	6.2	3	18.5				
	(4.0)	1	4				
	3.3	2	6.5	35	3	11.7	
C. S.	3.7	5	18.5				67
	6.3	3	19				
	(3.0)	2	6	43.5	3.5	12.5	

The urobilin excretion following operation is unquestionably the result of blood destruction and its significance will be discussed shortly, but first it is of interest to explore certain quantitative relationships between fall in hemoglobin and the excretion of urobilin. The simplest manner of expressing this relationship is to add up the total units of urobilin index during the period of observation and divide by the total fall in gms. per 100 c.c. of hemoglobin. Twelve cases were found suitable for this calculation and the results are summarized in Table II. Where figures are lacking for a short period, probable values for the index are estimated by interpolation, and in three instances extrapolation has been used. These interpolated or exterpolated values are in parentheses, and it may be seen that the possible error from doing this is not significant.

Two assumptions are implicit if we are to assign any value to the results of this calculation—namely, 1) that the blood volume remains relatively constant, and 2) that blood formation has virtually ceased or is not occurring to an extent that would interfere with our interpretation.[3] The second assumption, as we have seen, is probably a

[3] An indeterminate source of error arises of course from the possibility of blood loss. As we have seen this was of relatively minor significance when we were discussing total reduction of cell mass in relation to urobilin excretion before opera-

valid one. The first is, of course, unwarranted, but the figures might give some idea of how unwarranted if we knew how much urobilin excretion to expect from the destruction of a given amount of hemoglobin.

We actually have two independent ways of reaching such a figure. In a paper published some years ago, on the basis of personal observation and figures from the literature, the author calculated that the normal daily excretion of urobilin amounted on the average to 0.2 mgs. per gm. of circulating hemoglobin (2). Since the red cell has a normal life of about 120 days (3, 9, 10, 11, 12), this would mean the destruction of 1 gm. of hemoglobin should yield 120 × .2 or 24 mgs. urobilin excretion. From these figures, we may calculate the number of units of urobilin excretion to be expected from the destruction of 1 gm. per 100 cc. of hemoglobin which, in the absence of blood formation, is equal to a fall of 1 gm. in the determined hemoglobin percentage.

Total circulating hemoglobin is equal to $\frac{\text{blood vol.}}{100}$ times the Hgb. expressed in grams per 100 cc. This multiplied by .2 gives the expected urobilin excretion (2). Under normal conditions this excretion is defined as 1 unit. Therefore: $\frac{\text{blood vol.}}{100} \times 15 \times .2 =$ normal daily urobilin excretion (1 unit). (Equation A)

Since 1 gm. of hemoglobin yields 24 mgs. of urobilin excretion, the total urobilin yielded by the destruction of 1 gm. of hemoglobin per 100 cc. of blood $= \frac{\text{blood vol.}}{100} \times 24$. (Equation B)

$$\text{Dividing B by A: } \frac{\frac{\text{B.V.}}{100} \times 24}{\frac{\text{B.V.}}{100} \times 15 \times .2} = 8$$

tion. In considering the relationship between fall in hemoglobin percentage and urobilin excretion this loss is no longer of ninor significance. It is true that the major fall in red cells took place within the first few days after operation, but is what one would expect in the case of blood destruction as well as loss by hemorrhage. It is my impression gained at the time of the study that only one or two of these patients had a sufficient degree of blood loss to render the calculations that follow of doubtful significance.

Therefore 8 units of urobilin should normally be derived from the destruction of 1 gm. per 100 cc. of hemoglobin.

Cruz, Hawkins and Whipple (4), on theoretical grounds, have given the amount of bilirubin to be expected from the destruction of 1 gm. of hemoglobin as about 35 mgs. Using this figure instead of 24 in the above calculation gives about 11.5 units as the expected figure. Since it is improbable that 100% of the derived urobilin would be recovered in the analysis of the stools, I have preferred to use the lower figure obtained as the result of observations on stool urobilin excretion.

The figures given in Table II vary within a fairly narrow range—between about 10 and 12 units, with two exceptions.[4] Although it is gratifying that the determined and calculated figures are not far apart, one cannot say much about blood volume, except that this evidence indicates no extreme change.

In Chart 3, the urobilin units per gram per cent of hemoglobin loss are plotted against the preoperative hematocrit values. The fact that the figures are above the normal range indicates that the destruction of blood is greater than is accounted for by our calculated loss of hemoglobin, and therefore points to the presence of an increased blood volume before operation. Whether there is a correlation between the urobilin units and hematocrit is not clear from the chart: more figures for the upper and lower hematocrit range are needed to be certain. There is, however, some appearance of one, indicating that the highest blood volumes are obtained at the lower hematocrit range, and that the higher hematocrit values are obtained at the expense of a reduction in plasma volume. This coincides with the findings of Cassels and Morse (6), and suggests that if polycythemia is a necessity in these cases, it is produced only up to a certain degree by increase in cell mass and that beyond this point, further increase in blood

[4] It may be noted in these calculations that the possible net change in hemoglobin mass during operation has not been taken into account. In the discussion of this source of uncertainty a discrepancy of 100 cc. of blood was taken as the probable upper limit, corresponding to about one twentieth of the total blood volume or about 1 gm. per 100 cc. of hemoglobin loss. This figure will give some idea of the size of the error which is being disregarded. It may be seen that this will not invalidate the conclusion to be reached as a result of the calculations.

volume is avoided by decrease in plasma volume. Hallock came to the same conclusion in his study (5).

The similarity of the course of events to what happens in the newborn period (13, 14) is obvious—the fall in red cells and hemoglobin, the rise in urobilin excretion, the fall in reticulocytes to well below the normal figure. The differences are largely quantitative and in certain of the time relations. After birth the changes are not noticeable until after about a week or ten days, after operation they were immediate. The relative increase in urobilin excretion was considerably

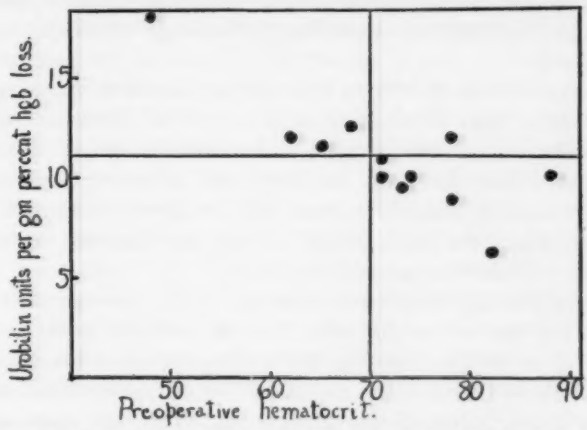

CHART 3. RELATION OF PREOPERATIVE HEMATOCRIT TO AMOUNT OF UROBILIN EXCRETED PER UNIT REDUCTION OF HEMOGLOBIN

greater but lasted a much shorter time after operation than in the newborn. There was no period of low hemoglobin and red cell levels analogous to the physiological anemia of early life, though it is interesting that the few instances of slightly subnormal hemoglobin levels all occurred in the younger patients. All these differences appear to be explicable as the result of differences in the capacity for adjustment, while the similarities appear to indicate that the mechanism of adjustment is essentially similar.

In discussing this mechanism in the case of the newborn, it was considered probable that the principal adjustment was in blood forma-

tion and that the blood destruction was a phenomenon which occurred at that period of life and helped reduce the hemoglobin levels, and although there was no evidence that it was harmful, still there was also no evidence that it was part of a physiological mechanism for reduction of hemoglobin and red cell levels. This point of view was in line with that prevailing at the time, namely, that while the rate of blood formation was controlled by some sort of acceleration-inhibition (homeostatic) mechanism, blood destruction normally included only the gradual wearing out of old red cells, while any increase above this low "normal" level was essentially pathological, and that the method the body had of meeting the challenge was simply to make more blood.

The similarity of the events recorded here to those occurring after birth, suggest that blood destruction as well as blood formation is under some sort of physiological or homeostatic control. By this I mean that when the body has more red cells than are necessary under the existing conditions, these cells are destroyed as part of the means by which the numbers are reduced, and that this destruction is not to be looked on as pathological.

The rise in blood destruction was not due to the operation itself. There is only one case in this series that can be considered as control—(S. M.) in whom the operation did nothing to relieve the anoxemia, and who showed none of the rise in urobilin excretion or fall in reticulocytes characteristic of the other cases. While one case of this sort does not constitute anything like adequate control, it can be augmented by an experience with urobilin excretion extending over twenty years during which in no case was operation of any sort attended by an increase in urobilin excretion amounting to more than one or two units at the most.

The idea that the rate of blood destruction is one of the physiological constants maintained by dynamic balance of accellerating and inhibiting factors is one that has recently been advanced. The evidence thus far is no more than suggestive, indicating the possibility that in some cases increased hemolysis may be dependent on the failure of some factor that normally inhibits blood destruction (15, 16, 17, 18, 19). The in vitro demonstration of some unidentified factor in plasma that inhibits the action of certain hemolysins may be of

significance, but thus far study has not demonstrated in vivo activity (20, 21, 22, 23). Suggestive evidence was obtained by the author some years ago. During early convalescence from various infections in which the rate of urobilin excretion had been increased, accompanied by fall in red cells and hemoglobin, there occurred a period of subnormal rate followed by a period of increased excretion during which the reticulocytes rose. This finding of a reduced rate of urobilin excretion during a period of reduced hemoglobin and red cells was similar to that of other observers (25, 26) who found what they called a "sparing" action on pigment excretion under similar conditions of reduced hemoglobin. We need not go into the question of whether or not the body can retain pigment for new blood formation. It may merely be pointed out that these observations may just as readily indicate an action on the part of the body by which blood destruction is reduced to compensate for the previous increased destruction. Such activity is in sense the converse of what occurs in the newborn period and in the cases reported here: In the one case blood destruction is reduced when there is need for increasing the red cells, in the other it is increased when there is necessity for reducing the red cells.

The significance of the observations recorded here is that they add one more bit of evidence that the rate of blood destruction is part of the physiological mechanism by which the constancy of the red cells and hemoglobin is maintained. Acceptance of the idea makes it necessary to reorient ourselves toward blood destruction as a controlled physiological process, not only in conditions like the one studied here, but also as part of the day to day normal blood destruction, and even in cases considered pathological.

SUMMARY

Twenty cases of tetralogy of Fallot were studied with the purpose of determining the rate of blood destruction and formation before and after operation. Relative rate of blood destruction was estimated from the average daily excretion of urobilin in the stools, that of formation from the reticulocyte counts.

1. Previous to operation both urobilin excretion and reticulocyte percentage were above normal. Taking into account the probable increase in cell mass, the relative increase in urobilin excretion indicates

a relative increase in blood destruction that approximately balances the increase in reticulocyte percentage.

2. Following operation the reticulocytes are diminished to a very low point and in many cases disappear entirely. This is interpreted to mean a marked reduction, if not a virtual cessation, of blood formation, presumably a part of the mechanism by which the preoperative polycythemia is reduced.

3. Following operation the urobilin excretion is markedly increased over a period of about a week, then rapidly falls to a normal figure.

4. Calculation of the ratio between the total urobilin excretion and the fall in hemoglobin indicates that the major factor in the reduction of red cells and hemoglobin following operation is blood destruction.

5. The similarity between the course of events in these cases and that during the reduction in hemoglobin and red cells in the newborn period is pointed out. As a result it is suggested that blood destruction in these cases is the result of a physiological mechanism which has as its "purpose" the reduction of red cells.

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PHYSIOLOGICAL STUDIES IN CONGENITAL HEART DISEASE

IX. Circulatory Dynamics in the Anomalies of Venous Return to the Heart Including Pulmonary Arteriovenous Fistula

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Previous publications from this laboratory have presented the methods used and the results of physiological studies in various types of congenital heart disease. This report will outline the results of physiological studies in thirty-eight anomalies of the venous return to the heart which have been seen in thirty-four patients during the past two years. Since many of these patients were studied in order to evaluate the possible efficacy of corrective surgical procedures, most of the anomalies of venous return were associated with other congenital cardiac defects. The incidence of abnormalities of venous return in this group therefore is no reflection of the incidence in the general population. In seven patients the only anomaly present was that of the cardiac venous return; hence the alterations of circulatory dynamics so produced may be more clearly elucidated and described in these patients.

Physiologically the anomalies of venous return may be classified in three groups:

I. Those constituting a right to left shunt:

A. Superior vena cava enters the left auricle

B. Pulmonary arteriovenous fistula

II. Those constituting a left to right shunt:

A. Systemic arteriovenous fistula

B. Pulmonary veins entering the right auricle or its tributaries

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III. Those constituting no shunt:

Left superior vena cava entering the right auricle or its tributaries.

METHODS

The methods employed in this study have been described in detail in the first paper of this series (1). In the interest of clarity, the terms and formulae used in the determination of various volume flows utilizing the Fick principle are redefined and restated at this point.

1. The systemic blood flow is the volume of blood passing through the peripheral vessels per minute.

$$\text{Systemic flow (ml. per min.)} = \frac{O_2 \text{ uptake (ml. per min.)} \times 100}{O_2 \text{ content of peripheral arterial blood (vol. \%)} - O_2 \text{ content of mixed venous blood (vol. \%)}}$$

2. The pulmonary artery blood flow is the volume of blood passing through the pulmonary artery per minute.

$$\text{Pulmonary artery flow (ml. per min.)} = \frac{O_2 \text{ uptake (ml. per min.)} \times 100}{O_2 \text{ content of pulmonary vein blood (vol. \%)} - O_2 \text{ content of pulmonary artery blood (vol. \%)}}$$

3. The effective pulmonary blood flow is the volume of mixed venous blood which, after returning to the right auricle, eventually reaches the pulmonary capillaries.

$$\text{Effective pulmonary flow (ml. per min.)} = \frac{O_2 \text{ uptake (ml. per min.)} \times 100}{O_2 \text{ content of pulmonary vein blood (vol. \%)} - O_2 \text{ content of mixed venous blood (vol. \%)}}$$

4. The *overall* shunt is the difference in the volume of the pulmonary artery and systemic blood flows which has resulted from shunting. It is equal to the difference between the volumes of the total left to right and the total right to left shunt.

Overall shunt (left to right) = pulmonary artery flow − systemic flow
Overall shunt (right to left) = systemic flow − pulmonary artery flow

5. The *total* left to right shunt is the volume of fully oxygenated blood which is shunted into the pulmonary circulation per minute.

Total left to right shunt = pulmonary capillary flow − effective pulmonary flow

In the absence of collateral circulation to the lung the pulmonary capillary flow equals the pulmonary artery flow.

6. The *total* right to left shunt is the volume of mixed venous blood which is shunted into the systemic circulation per minute.

Total right to left shunt = systemic flow − effective pulmonary flow

In calculating flows from these formulae it is necessary to make certain assumptions. The oxygen content of pulmonary vein blood cannot usually be measured directly. When this is the case, and in the absence of significant pulmonary disease, the saturation of the pulmonary vein blood is assumed to be 96 per cent. This assumption is based on a review of the values obtained for the oxygen saturation of pulmonary vein blood in twenty-four patients in whom pulmonary vein blood was obtained by direct catheterization in this laboratory. The mean pulmonary vein blood oxygen saturation in this group was 95.7 per cent with a standard deviation of 2.7 per cent.

Mixed venous blood was obtained from the pulmonary artery except in the presence of a left to right shunt, in which case blood from the chamber or vessels immediately proximal to the site of the shunt was assumed to be representative of mixed venous blood. In those cases in which the pulmonary artery could not be catheterized, in whom the pulmonary artery was believed to arise from the right ventricle, and in whom no patent ductus arteriosus was clinically suspected, the oxygen content of pulmonary artery blood and of right ventricular blood were assumed to be identical.

Blood was obtained by cardiac catheterization and arterial puncture. Blood oxygen contents were determined manometrically by the method of Van Slyke and Neill (2). Expired air was collected in Douglas bags. The carbon dioxide content was determined in the Haldane apparatus (3), and the oxygen content was determined with the Pauling oxygen analyzer. All gas volumes were expressed in terms of dry gas at 760 mm. Hg and zero degrees centigrade. Intracardiac pressures were measured by means of strain gauges and optically recorded by oscillograph galvanometers. Mean pressures were calculated by planimetric integration of the area under the pressure curves. Pulmonary and systemic peripheral resistances were approximated by means of a simplified version of Poiseuille's formula (4).

$$7.\ \text{Resistance (mm. Hg./L/min./M}^2\text{)} = \frac{\text{mean pressure fall (mm. Hg)}}{\text{Blood flow (liters/min/M}^2\text{)}}$$

Since the mean left auricular pressure cannot be measured in a majority of patients, the mean pulmonary artery pressure alone was used as the numerator in equation 7. The upper limit of normal pulmonary resistance calculated in this way is 5 mm. Hg/L/min./M^2. An elevation of this value may be due to an increase in pulmonary vascular resistance, to elevation of the left auricular pressure, or to an elevation in the hematocrit.

This latter factor elevates vascular resistance by increasing the viscosity of blood. Whittaker and Winton (5) have quantitated this factor by perfusion experiments in the isolated hindlimbs of dogs. These workers determined the relationship of the apparent viscosity of bloods of various hematocrits to the viscosity of blood with a hematocrit of 48 (viscosity ratio). By recalculating their data for a normal hematocrit of 45, a curve relating the hematocrit to the viscosity ratio was constructed (fig. 1). When the vascular resistance, as calculated from formula 7, is divided by the viscosity ratio obtained from figure 1, a figure is obtained which expresses the resistance to flow of blood with a normal hematocrit of 45. Allowance could not be made for variations in the apparent viscosity of blood due to changes in the diameter of vessels or the rate of blood flow. All the vascular resistances calculated in this paper have been corrected for a hematocrit of 45.

RESULTS

I. Conditions constituting a right to left shunt

A. Superior vena cava enters the left auricle. Four patients were studied in whom catheterization indicated that a superior vena cava drained into the left auricle. In three cases this impression was substantiated by angiocardiography. In the fourth case, no angiocardiogram was done. In no instance was this anomaly present without other congenital cardiac defects.

Case. 1. T. B., This 4½ year old boy was not cyanotic at birth, but became definitely so by 10 months of age. Short periods of unconsciousness were noted at the

age of 5 weeks during a bout of pertussis. Between the ages of 2 and 3½ years, periods of unconsciousness occurred approximately once a month. Physical activity was markedly restricted by exertional dyspnea. Squatting was frequent.

Physical examination: The patient was well nourished, but markedly cyanotic and there was suffusion of the conjuctivae. The left chest bulged slightly. The pulse rate was 100 per minute and regular. The blood pressure was 80/70 in the arms and 90/75 mm. Hg. in the legs. A systolic thrill and a harsh, grade 3, systolic murmur were present, being maximal over the third left intercostal space.

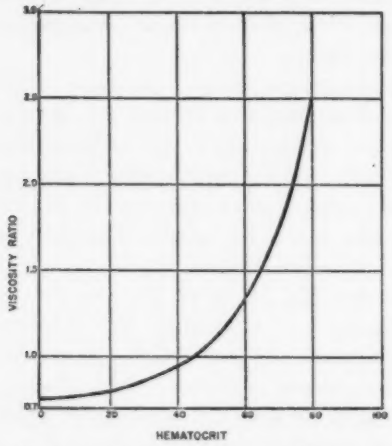

FIG. 1. THE RELATIONSHIP BETWEEN THE HEMATOCRIT AND THE VISCOSITY RATIO

The viscosity ratio is determined by dividing the apparent viscosity of the patient's blood by the apparent viscosity of blood with a hematocrit of 45. The data of Whittaker and Winton (Ref. 5) were recalculated in the construction of this curve.

Fluoroscopy revealed situs inversus with levocardia and a right aortic arch. The heart was normal in size, there was slight concavity in the region of the pulmonary conus, and the lung fields appeared normal. Marked right axis deviation was present.

The hemotocrit was 70, the red blood count 9.05 million, and the hemoglobin was 20 grams per cent.

Physiological studies: The patient's heart was catheterized from both the left and right median basilic veins. The data obtained are summarized in table I. When the catheter was introduced from the left arm,

TABLE I

CASE NUMBER	NAME	AGE	SEX	SURFACE AREA (M^2)	O_2 CONSUMPTION, CC. PER MINUTE	O_2 CONTENT VOLS. % (PRESSURE MM. Hg BELOW)										BLOOD FLOW CC./MIN./M^2			SHUNT CC./MIN./M^2		
						Rt. SVC	Rt. aur.	Rt. vent.	Pul. art.	Pul. vein (calc.)	L. SVC	L. aur.	L. vent.	Fem. art.	O_2 cap.	Sat. %	Pul.	Eff. pul.	Syst.	L-R	R-L	Overall
1	T. B.	4	M	0.6	60	15.4	15.3	15.1 80/12		25.4	10.3	20.4 25/11	19.9 129/8	19.9	26.5	75	970	970	2080	0	1110	1110 R-L
2	G. C.	9	M	1.05	134					29.6 (cath)	20.5	25.4 6/2	22.1 100/3	20.5 105/86	31.7	65						
3	D. C.	8	M	0.87	131	13.2	18.9 20/15	19.7 25/8		23.6 (cath)	16.3	20.6	20.0 79/37	18.4	24.6	75	3860	2070	7340	1790	5270	3480 R-L
4	P. M.	18	F	1.40	170	13.1	—			24.7		21.6 23/18	21.1 117/3	Aorta 19.5 100/78	25.7	76		1050	1900		850	

Data obtained from cardiac catheterization of four patients in whom a left superior vena cava drained into the left auricle.

it was seen to enter the left auricle where highly oxygenated blood was obtained. It then entered the left ventricle where the high oxygen content of the blood and the high systolic pressure were comparable with figures obtained from the femoral artery. This indicated that a left superior vena cava was present which drained into the left auricle. There was no evidence of intracardiac right to left shunt. When the catheter was introduced from the right arm, it passed into the right auricle and ventricle, but the pulmonary artery could not be entered. Blood oxygen contents from the right heart indicated no intracardiac

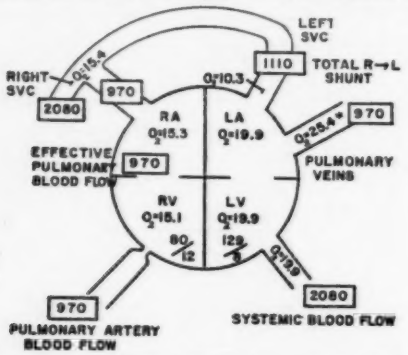

FIG. 2. DIAGRAM OF THE FLOW RELATIONSHIPS IN CASE 1 (T. B.)

Pulmonic Stenosis was present in addition to two superior venae cavae, one of which drained into the left auricle.

left to right shunt. The elevated right ventricular pressure, together with the very low pulmonary artery and effective pulmonary blood flows, indicated the probable existence of pulmonic stenosis. The right to left shunt which accounted for the peripheral arterial oxygen saturation of 75 per cent was attributed to the anomalous drainage of a left superior vena cava into the left auricle. The flow relationships are diagrammed in figure 2.

Angiocardiography was performed by Dr. R. Cooley from the department of radiology. When the dye was introduced through the right jugular vein it outlined the right auricle, ventricle, and pulmonary artery. When the dye was introduced through the left jugular vein the left auricle, ventricle and aorta were opacified.

The patient was operated on by Dr. A. Blalock, the approach being from the right, and hence the anomalous left superior vena cava was not seen. A successful

subclavian to right pulmonary artery anastomosis was established. The patient had an uneventful postoperative course, his cyanosis markedly decreased, and he developed a normal exercise tolerance.

Comment: This patient represents a case of pulmonic stenosis, situs inversus with levocardia, a right aortic arch, and the anomalous drainage of a left superior vena cava into the left auricle. The peripheral arterial unsaturation so produced allowed the patient to benefit from the production of an artificial ductus arteriosus since the ratio of the effective pulmonary flow to the systemic blood flow, could be increased (6). The volume of the right to left shunt in this patient is surprisingly large and might lead one to suspect the presence of a ventricular septal defect with overriding of the aorta. However, in the presence of a systolic pressure of 80 mm. Hg in the right and 129 mm. Hg in the left ventricle, one would expect some degree of left to right admixture of blood in the presence of a ventricular septal defect. However, no evidence of any intracardiac shunting was found by catheterization. Furthmore, angiocardiography revealed no dextroposition of the aorta.

Case 2. G. C. Clinically, this patient was believed to represent a case of situs inversus with levocardia and the Tetralogy of Fallot. The results of cardiac catheterization are presented in table I. The oxygen content of blood from the auricle and ventricle which were entered were higher than that from the femoral artery and the systolic pressure in the ventricle was comparable to that of the femoral artery. Therefore it was suspected that the left auricle and ventricle had been intubated. Angiocardiograms performed by Dr. R. Cooley, demonstrated the dye entering the left auricle through a left superior vena cava, thence passing anteriorly into a large chamber, out the aorta and, to a lesser extent, out the pulmonary artery. The five volume per cent decrease in oxygen content of blood between the left auricle and femoral artery is evidence of an intracardiac right to left shunt of considerable magnitude, probably through a ventricular septal defect into an overriding aorta. Although no flows could be calculated, it was felt that the data tended to substantiate the clinical impression of the Tetralogy of Fallot. A subclavian to pulmonary artery anastomosis was done with excellent results. Since the surgical approach was from the right, the anomalous

left superior vena cava was not visualized. In summary, this was a case of situs inversus with levocardia, the Tetralogy of Fallot, and an anomalous left superior vena cava draining into the left auricle. As a result, blood from the left auricle was only 80 per cent saturated with oxygen. The volume flows could not be calculated since no mixed venous, right ventricular or pulmonary artery blood samples were obtained.

Case 3. D. C. This patient was catheterized through both the right and left antecubital veins. The results are recorded in table I. When the catheter was passed from the right side it entered the right auricle through the right superior vena cava and appeared to pass directly into the right lung field by way of a pulmonary vein. Blood from the pulmonary vein was 96 per cent saturated with oxygen. The oxygen content of right auricular blood was 5.7 volumes per cent higher than that of the superior vena cava, indicating that one or more pulmonary veins entered the right auricle and that in addition, an auricular septal defect might be present. The right ventricle could not be entered. When the catheter was introduced from the left arm it appeared to enter the left auricle and ventricle. The systolic pressure and oxygen content of this ventricle were comparable to those of the femoral artery. The catheter was also passed through an auricular septal defect into the right auricle, the right superior vena cava, and the right ventricle. The right ventricular pressure was normal. When the volume flows were calculated from the figures obtained by cardiac catheterization, the effective pulmonary blood flow was seen to be slightly reduced (2.07 L/min./M^2). The pulmonary artery flow was higher than normal (3.86 L/min./M^2) due to the left to right shunt produced by the auricular septal defect and the drainage of one or more pulmonary veins into the right auricle. The systemic blood flow was markedly elevated (7.34 L/min./M^2) due to a large right to left shunt, some of which may have been through the auricular septal defect. It was probable that most of the right to left shunt was through the left superior vena cava entering the left auricle. Angiocardiography was performed by Dr. Sloane. Injection of the dye into the left external jugular vein demonstrated radio-opaque material entering the left auricle through a left superior vena cava and then opacified simultaneously both the right auricle and

the left ventricle. In summary, this is a patient with an auricular septal defect, with one or more pulmonary veins emptying into the right auricle, and with an anomalous left superior vena cava draining into the left auricle. No surgical treatment was advised.

Case 4. P. M. This patient was believed to have dextracardia, although the marked cardiac enlargement and some atypical features of the electrocardiogram made it impossible to be sure that true dextracardia was present. This also made it difficult to determine by fluoroscopy which of the cardiac chambers had been catheterized. From the data presented in Table I it may be seen that the catheter passed down a right superior vena cava into an auricle in which the blood oxygen content was 8.5 vol. per cent higher than that of the superior vena cava. From this auricle the catheter entered a ventricle in which the blood oxygen content was similar to that of the auricular blood, and then entered the aorta. The systolic pressure and blood oxygen content of the aorta were similar to those of this ventricle. The systemic, and particularly the effective pulmonary blood flows were lower than normal (1.90 and 1.05 L/min./M^2 respectively). The pulmonary artery flow could not be calculated since the pulmonary artery was not catheterized. It was believed that this patient was a case of dextrocardia with an anomalous right superior vena cava draining into the left auricle and in addition, some other cardiac anomaly the exact nature of which could not be ascertained. This case illustrates the difficulties which may be encountered in interpreting the results of cardiac catheterization.

Comment: Three proven cases in which a left superior vena cava entered the left auricle have been presented. In a fourth case, with dextrocardia a right superior vena cava drained into the left auricle. There are three indications that the catheter has entered the left auricle through an anomalous superior vena cava. They are: the fluoroscopic appearance of the catheter, the marked increase in oxygen content of the auricular blood as compared with the vena caval blood (the increase averaging 7.0 vol. per cent in these cases), and the similar systolic pressures in the ventricle entered and in a systemic artery. It must be pointed out, however, that any or all of these criteria may

occasionally be found in other congenital cardiac abnormalities and that proof of the existance of anomalous drainage of a superior vena cava into the left auricle can thus far be obtained only by angiocardiography or by direct visualization. The anomaly under discussion produces a right to left shunt causing the systemic blood flow to exceed the effective pulmonary blood flow and hence causing peripheral arterial unsaturation. The extent and importance of the hemodynamic changes produced by this anomaly alone cannot be assessed in the cases reported here, since all of them presented additional complicating congenital cardiac anomalies. In the first case, the extracardiac right to left shunt produced by the anomalous drainage of the left superior vena cava made treatment possible by the creation of an artificial ductus in a case of otherwise pure pulmonic stenosis. It is of interest that three of the four patients with anomalous drainage of a superior vena cava into the left auricle also had an anomaly of the cardiac position consisting of dextrocardia or situs inversus with levocardia.

B. Pulmonary arteriovenous fistula. Anatomically the existance of a pulmonary arteriovenous communication does not constitute an anomaly of the cardiac venous return. However, this condition produces a right to left extracardiac shunt allowing unoxygenated blood to enter the left auricle and producing peripheral arterial unsaturation. Physiologically, therefore, it may be classified as an anomaly of the venous return to the left auricle.

Since the description by Rodes in 1938 (8), the clinical syndrome of pulmonary arteriovenous fistula has been recognized with increasing frequency. Several years later, Hepburn and Dauphinee (9) reported the successful treatment of this condition by the surgical removal of a pulmonary hemangioma and thereby created widespread interest in the detection and treatment of further cases (10 to 15). Yater, Finnegan and Griffin (16) recently reviewed the clinical findings in forty-five patients. Maier, et al. (13) described the results of physiological studies in a case of pulmonary arteriovenous fistula. The significant findings were the peripheral arterial oxygen saturation of 74 per cent, a normal systemic blood flow, a pulmonary arteriovenous shunt amounting to 58 per cent of the pulmonary blood flow, and normal pressures in the right auricle, ventricle, and pulmonary artery.

The results of cardiac catheterization in one patient with a large

pulmonary arteriovenous fistula have been reported by Baker and Trounce (17). In contrast to the findings in the patient described by Maier et al. (13), this patient had an elevated cardiac output of 12.10 L/min. (7.73 L/min./M^2) and there was slight cardiac enlargement. The effective pulmonary blood flow in this patient was 2.60 L/min. (1.65 L/min./M^2). Thus, 79 per cent of the right ventricular output was shunted through the arteriovenous fistula. The mean pulmonary artery pressure was 13.5 mm. Hg.

Four cases of proven pulmonary arteriovenous fistula have been studied in this laboratory.

Case 5. F. P. The first patient was a 24 year old male who was referred by Dr. I. J. Pincus of Philadelphia for study and treatment of multiple pulmonary hemangiomata. The patient's general health had been good except for repeated upper respiratory infections. There had been no cough or hemoptysis. Cyanosis and exertional dyspnea were first noted at the age of 10 years, but normal activity was continued until the patient was of high school age. At this time clubbing appeared and he was told to reduce his physical activity. Because of increasing cyanosis, dyspnea and clubbing, the patient was studied by Mackler and Zion at the age of 21 years. Their findings have been reported in detail (11). A diagnosis of multiple pulmonary hemangiomata was made on the basis of the clinical findings, chest films, and the fluoroscopic appearance of the masses seen during the Valsalva maneuver. Since the time of these studies, his symptoms remained unchanged save for several transient episodes of numbness of the left side of the face and left arm without loss of motor power.

Physical examination: The patient was a moderately cyanotic young man who was not dyspneic at rest. The pulse rate was 80, the respiratory rate 18, and the blood pressure 96/60. There was marked clubbing of the fingers and toes and suffusion of the conjunctivae. A pea-sized angioma was present on the right side of the neck. A systolic and diastolic bruit was audible over the right lung base posteriorly. On physical examination, the heart was normal and the neck veins were not distended. No edema was present.

The hemoglobin was 22.3 grams, the red blood count 6.80 million, and the hematocrit 66. The vital capacity was 3.8 liters, the circulation time (decholin) 17 seconds, and the venous pressure, 55 mm. of saline. Roentgenological studies demonstrated three pulmonary opacities which were located in the left upper lobe, in the apex of the right lower lobe, and at the base of the right lower lobe posteriorly. These were again seen to decrease in size when the Valsalva maneuver was done, as had been previously noted by Mackler and Zion (11).

Physiological studies: From the data as summarized in table II, it was apparent that no intracardiac left to right shunt existed. The right

TABLE II

CASE NUMBER	NAME	AGE	SEX	SURFACE AREA (M^2)	O_2 CONSUMPTION, cc./min.	O_2 CONTENT (VOLS. %)								BLOOD FLOW			SHUNT		MEAN PA PRESSURE MM. Hg	HEMATOCRIT	VISCOSITY RATIO	PULMONARY RESISTANCE		
						SVC	Rt. aur.	Rt. vent.	Pul. art.	Pul. vein (calc.)	Fem. art.	O_2 cap.	% sat.	Pul.	Eff. pul.	Syst.	Total R-L	% PA flow				Total	Lung excl. A-V sat.	A-V sat.
5	F. P.	24	M	1.80	239	18.4	19.8	20.7 28/11	19.9 24/14	26.6	23.8	27.7	86	3400	1980	3400	1420	42	17	66	1.54	3.2	5.6	7.8
6	S. X.	15	M	1.18	122	18.2	18.0	19.0 26/9	Assumed 26/16	32.6	23.0	33.9	68	2580	760	2580	1820	71	19	79	2.43	3.0	9.7	4.3
7	H. M.	28	F	1.41	210	18.0 IVC 20.4	20.4 12	17.8 32/8	17.8 32/19	32.6	21.4	34.0	63	4170	1010	4170	3160	76	23	77	2.17	2.5	10.5	3.4
34	C. S.	8	F	0.97	97	13.7 IVC 14.0	13.5	13.1 27/9	13.4 27/16	19.9	15.9	20.7	77	3880	1530	3880	2350	61	20	53	1.14	4.5	11.5	7.5

Summary of data obtained in four patients with pulmonary arteriovenous fistula.

ventricular and pulmonary artery pressures were normal. The peripheral arterial oxygen saturation was 86 per cent. The flow relationships are illustrated in Figure 3. The systemic blood flow was 3400 cc./min./M². It is apparent that the effective pulmonary blood flow, as calculated from the oxygen content of blood from the pulmonary artery and that of a pulmonary vein assumed to be 96 per cent saturated, represents the volume of flow through the pulmonary capillary bed. Assuming a diagnosis of pulmonary arteriovenous fistula, the oxygen content of blood as it enters the left auricle must equal that of the

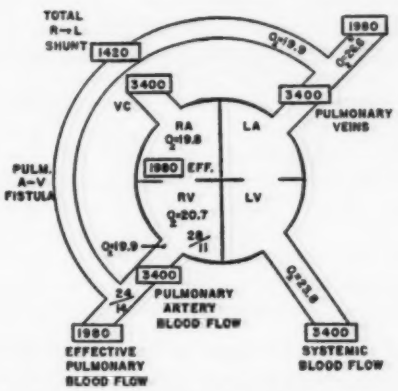

FIG. 3. DIAGRAM OF THE CIRCULATORY FINDINGS IN CASE 5 (F. P.) WHO HAD A PULMONARY ARTERIOVENOUS FISTULA

The cardiac output was normal despite the fact that 42 per cent of the pulmonary artery flow was shunted through the fistula.

systemic arterial blood. Hence, the pulmonary artery blood flow equals the systemic blood flow. The difference between the pulmonary artery blood flow and the effective pulmonary blood flow represent the volume of blood shunted through the pulmonary arteriovenous fistula (1420 cc./min./M²). In this patient 42 per cent of the right ventricular output coursed through the fistula. Despite the presence of the pulmonary arteriovenous fistula, the total pulmonary and systemic blood flows were not elevated. This is in agreement with the findings in the case reported by Maier et al. (13). The vascular resistance of the arteriovenous

fistula, of the remaining pulmonary vessels, and of the total pulmonary vascular bed may be approximated by means of formula 7. This may be accomplished by using the total right to left shunt to calculate the resistance of the arteriovenous fistula and using the effective pulmonary blood flow to compute the resistance of the remainder of the pulmonary bed. In this case, the total pulmonary resistance was normal, the resistance of the lung exclusive of the fistula was slightly elevated, and the

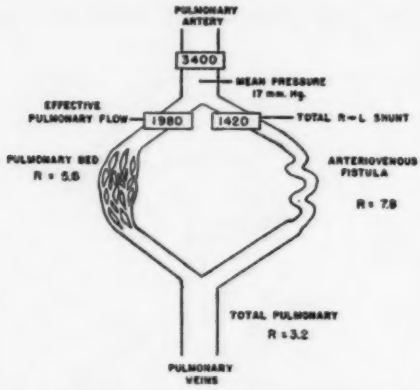

FIG. 4. DIAGRAM OF THE RELATIONSHIP OF PRESSURE, CORRECTED VASCULAR RESISTANCES, AND FLOWS IN CASE 5 (F. P.) IN WHOM A PULMONARY ARTERIOVENOUS FISTULA WAS PRESENT

The total pulmonary resistance was normal while the resistance of the lung exclusive of the fistula was elevated.

resistance of the pulmonary arteriovenous fistula was almost twice the normal pulmonary resistance (Fig. 4).

At thoracotomy, the two arteriovenous aneurysms in the right lower lobe were seen and this lobe was removed. Injection studies of the operative specimen revealed two large arteriovenous aneurysms and in addition, numerous small arteriovenous communications throughout the remainder of the lobe. Subsequent to operation, the patient felt improved, the cyanosis and dyspnea decreased, but the clubbing was unchanged. One year following the first operation the hematocrit had fallen from 66 to 56, but the arterial oxygen saturation was still 85 per cent. Chest films revealed the previously noted mass in the base of the left upper lobe. Accordingly, a segmental resection of this portion of the left upper lobe was done.

The postoperative course was uneventful. Unfortunately, the arterial oxygen saturation was not determined following the second operation. It may be expected, however, that the multiple small arteriovenous communications will prevent complete alleviation of the patient's disease by surgical excision of the grossly visible lesions.

Case 6. S. X. The patient was a 15 year old male child whose early development had been normal. Cyanosis was first noted at the age of 5 years and gradually increased until the time of admission to the hospital. He also developed clubbing of the fingers and exertional dyspnea which was sufficient to require rest after climbing one flight of stairs. At the age of ten, a pulsating lump on the right side of the forehead was noted. He never squatted when tired.

Physical examination: The patient was a poorly developed boy who exhibited moderate dyspnea on exercise. The respiratory rate was 26, the pulse rate 90, and the blood pressure 84/60 in the arms and legs. Marked clubbing and cyanosis were present and the conjunctivae were suffused. The heart was not enlarged on physical examination and no murmurs were present. A small hemangioma was present on the left side of the forehead.

The red blood count was 9.30 million, the hemoglobin 25.3 grams, and the hematocrit 79.5. Electrocardiography revealed right axis deviation. Roentgenological studies demonstrated clear lung fields with normal pulsations. The heart was normal in size, but there was slight straightening of the left cardiac border. Angiocardiograms performed by Drs. Cooley and Sloane indicated the abnormally rapid passage of the dye through the lungs. A 1 x 1½ cm. opacified area was noted near the hilum of the right lung and was thought to represent a pulmonary arteriovenous aneurysm.

Physiological studies: The results of cardiac catheterization are outlined in Table II. No evidence of left to right intracardiac shunt was present and the right ventricular systolic pressure was normal. The pulmonary artery was not entered. For purposes of caculation, the pulmonary artery blood oxygen content and systolic pressure were assumed to be the same as those of the right ventricle. An arbitrary pulmonary arterial diastolic pressure was assumed. The arterial oxygen saturation of 68 per cent indicated the presence of a sizeable right to left shunt which in this instance was 71 per cent of the right ventricular output. It may be seen that the systemic and pulmonary blood flows were within normal limits (2,580 cc./min./M^2) while the effective pulmonary blood flow was markedly decreased (760 cc./min./M^2) by the large volume of shunt through the pulmonary arteriovenous communication. The total pulmonary resistance was normal. The vascular resistance of the lung exclusive of the fistula was twice the normal value.

This was compatible with the finding of a fall in the oxygen consumption per liter of ventilation during the standard breathing exercise test (6). The resistance of the arteriovenous fistula was equal to that of a normal pulmonary vascular bed.

At operation, a large, approximately thumb-sized communication was seen which arose from a branch of the left pulmonary artery and coursed into the left auricle. This was ligated and divided, following which there was an immediate and dramatic improvement in the patient's color. One year later, the patient was asymptomatic and the peripheral arterial oxygen saturation had risen to 93 per cent.

Case 7. H. M. This patient was a 26 year old woman who was thought to be normal at birth. Cyanosis and exertional dyspnea were first noticed at the age of 1½ years. As a child the patient could walk only one block and has always preferred to sit in the knee chest position. Gradually, the patient's exercise tolerance increased until she was able to walk five or six blocks slowly. At the age of 16 years she developed polyarthritis which was accompanied by generalized edema. The edema returned following a tooth extraction at the age of 22 and occurred again, in conjunction with oliguria, at the age of 25. On the latter occasion the edema disappeared when she received supplementary protein feedings.

Physical examination: The patient was a small, thin, poorly nourished woman who exhibited moderately severe cyanosis and clubbing of the fingers and toes. The pulse rate was 80 and the blood pressure 104/80. The apex impulse was in the fifth left intercostal space in the midclavicular line. The pulmonic second sound was accentuated, but no murmurs were present. The lungs were clear to auscultation. The abdomen was normal. No edema and no cutaneous hemangiomata were seen.

The red blood count was 8.85 million, the hemoglobin was 25 grams, and the hematocrit was 77. The NPN was 49 mgm. per cent. Fluoroscopy revealed moderate cardiac enlargement with a prominent pulmonary conus and vigorously pulsating arteries. An accentuation of vascular markings was seen in the right lower lobe. The circulation time (decholin) was 9 seconds. The electrocardiogram revealed right axis deviation in the conventional limb leads with left ventricular preponderance in the precordial leads.

Physiological studies: From the data summarized in Table II it may be seen that there was no evidence of a left to right intracardiac shunt. The marked systemic arterial unsaturation, however, indicated a sizable right to left shunt which in this case amounted to 3160 cc./min./M^2, or 76 per cent of the pulmonary blood flow. These findings, with the normal right ventricular pressure, lead to a presumptive diagnosis of an intrapulmonary shunt. The pulmonary and systemic blood flows

in this patient were elevated (4170 cc./min./M²). The pulmonary artery pressure was at the upper limits of normal. The total pulmonary resistance was slightly below normal (2.5 mm. Hg/L/min./M²). The resistance of the lung exclusive of the fistula was twice the normal value. In this patient the resistance of the arteriovenous fistula was 3.4 mm. Hg/L/min./M². This is lower than the value obtained in either of the previous cases. It was of particular interest that this patient had an increased cardiac output and moderate cardiac enlargement, neither of which had been seen in the two patients previously described.

At operation a large pulsating mass was seen which was confined to the right lower lobe and this lobe was removed. The patient's color improved immediately and several days following the procedure the arterial oxygen saturation was 97 per cent.

Case 34. C. S. This eight year old girl was thought to lack strength during infancy, but was otherwise normal until the age of seven. During the year prior to admission the patient developed increasing fatigability, dizziness, and exertional dyspnea. Cyanosis was noted for the first time several months prior to admission.

Physical examination: The patient was a thin child with obvious cyanosis of the lips and nails. The pulse rate was 100, the respiratory rate 23, and the blood pressure 90/60 mm. Hg. The heart and lungs were normal on physical examination. Moderate clubbing of the fingers and toes was present.

The red blood count was 6.10 million, the hemoglobin 17.0 grams, and the hematocrit 53. The circulation time was 10 seconds (decholin). Chest films revealed a round opacity 2 cm. in diameter in the right lateral mid-lung field posteriorly. The heart size was normal. The electrocardiogram revealed right axis deviation

Physiological studies: The data obtained from cardiac catheterization are summarized in Table II. As in the previous cases presented, there is no evidence of intracardiac left to right shunt. The arterial oxygen saturation of 77 per cent indicated a right to left shunt which was calculated to be 2350 cc./min./M² or 61 per cent of the right ventricular output. The systemic and pulmonary artery blood flows were 3880 cc./min./M² which is at the upper limit of normal. The pulmonary artery pressure was 27/16 mm. Hg. The total pulmonary resistance was normal (4.5 mm. Hg/L/min./M²) while the vascular resistance of the lung exclusive of the fistula was increased to more than twice the normal value (11.5 mm. Hg/L/M²).

At surgery a large arteriovenous fistula was seen in the right lower lobe and this lobe was removed. However, other smaller arteriovenous fistulae were seen in other portions of the lung.

Comment: Four patients with proven pulmonary arteriovenous fistulae have been discussed. All of them exhibited the cyanosis, clubbing, and polycythemia which are characteristic of the disease. In each instance catheterization revealed no evidence of an intracardiac left to right shunt. The right ventricular and pulmonary artery pressures were at the upper limits of normal. The femoral arterial oxygen saturation ranged from 63 to 86 per cent in these patients, indicating a right to left shunt. There was no evidence of pulmonary parenchymal disease or of a left to right intracardiac shunt. Furthermore, the presence of a right to left shunt through a patent foramen ovale caused by pulmonary hypertension or by pulmonic stenosis was excluded by the finding of a normal right ventricular pressure. The right to left shunt was therefore assumed to be through a pulmonary arteriovenous fistula. The percentage of the right ventricular output which passed through the fistula in these patients ranged from 42 to 76 per cent and averaged 62.5 per cent.

In three patients (# 5, 6, and 34) the pulmonary artery and systemic blood flows were normal and there was no cardiac enlargment. A normal cardiac output was also found in the patient catheterized by Maier, et al. (13). No cardiac enlargement was noted in the four patients reported by Maier, et al. (13). Rodes, (8) Hepburn and Dauphinee (9), and Watson (12).

It is well known that the presence of a *systemic* arteriovenous fistula decreases the total systemic resistance, resulting in an increased cardiac output. However, the vascular resistance of the lung is normally so low (3 to 5 mm. Hg/L/min./M^2) that the presence of a shunt in parallel with the pulmonary resistance does not significantly reduce the overall vascular resistance of the lung unless the resistance of the shunt is unusually low. Thus, in cases 5, 6, and 34 the total pulmonary vascular resistance averaged 3.6 mm. Hg/L/min./M^2, which is a normal value. The cardiac output in these patients was normal averaging 3290 cc./min./M^2. The vascular resistance of the lung exclusive of the fistula was increased in all four patients to an average figure of 9.3 mm. Hg/L./min./M^2 which is twice the normal value. This increased

resistance leads to an increase in the amount of right to left shunt, a decrease in the effective pulmonary blood flow, and hence to greater systemic arterial oxygen unsaturation. Similar increases in pulmonary resistance have been described in many congenital cardiac malformations (18). The reason for the increase in the vascular resistance of the lung exclusive of the fistula is not known. There is no reason to suspect an increased left auricular pressure in this condition. In addition, the effect of increased blood viscosity in elevating the calculated resistance has been eliminated by the method previously described. Two factors may play a role in elevating the resistance of the lung exclusive of the fistula. The first may be an anatomic increase in the pulmonary resistance due to multiple small pulmonary thrombi such as have been described in the Tetralogy of Fallot in which there is also polycythemia and a reduced effective pulmonary blood flow (19). The second factor may be pulmonary arteriolar constriction caused by hypoxemia. Such a mechanism has been described by Motley, et al. (20). If this is the case, a vicious circle may be established. Thus, peripheral arterial oxygen unsaturation augments the pulmonary arteriolar resistance, increases the blood flow through the fistula, and so further increases the peripheral arterial oxygen unsaturation.

In the fourth patient (# 7) the total pulmonary resistance was 2.5 mm. Hg/L/min./M^2. In this patient the cardiac output was elevated (4170 cc./min./M^2) and cardiac enlargement was present. It is of interest to compare the findings in patient number 7 with the data published by Baker and Trounce (17). These authors observed cardiac enlargement and an elevated cardiac output of 7730 cc./min./M^2. If the respective resistances are calculated from their data the total pulmonary vascular resistance is found to be reduced to 0.9 mm. Hg/L/min./M^2, and the resistance of the arteriovenous fistula is 1.1 mm. Hg/L/min./M^2. Cardiac enlargement was also found in the three other patients described by Sisson et al. (10), Wodehouse (14), and Boerma and Brilman (15). These findings demonstrate that the resistance of the pulmonary arteriovenous fistula may be sufficiently low to cause a significant reduction of the total pulmonary resistance, resulting in an increased cardiac output and cardiac enlargement. In the majority of patients however, cardiac enlargement has not been described. One may assume therefore, that in these patients the pulmonary arterio-

venous fistula does not decrease the total pulmonary resistance and that the cardiac output is not increased.

II. Conditions constituting a left to right shunt

A. Systemic arteriovenous fistula. A systemic arteriovenous fistula produces a left to right shunt allowing oxygenated blood to return to the right auricle. Physiologically, it may therefore be considered an anomaly of the venous return to the right auricle. The clinical features of systemic arteriovenous fistulae are well known. The hemodynamic changes produced have been described in detail by Cohen, Edholm, Howarth, McMichael, and Sharpey-Shaffer (21). One case is presented here in order to contrast the findings with those of pulmonary arteriovenous fistulae.

Case 8. J. K. This patient was a 23 year old male who entered the hospital because of swelling and pain in the left groin, thigh, and calf. Four years previously, while in the Army, he had received a chest wound. At that time there was some question as to whether or not the left groin was also injured. When he became ambulatory during convalescence, the patient noticed a bluish discoloration of the left leg with swelling of the calf and groin, and dull pain in these areas. The symptoms had become progressively worse during the four years prior to admission and, in addition, palpitation and exertional dyspnea had developed. There was no orthopnea or edema of the right leg.

Physical examination: The patient was a well developed and nourished male having no dyspnea at rest. The pulse was 75 and regular, the blood pressure 100/70, and the respiratory rate was 18. The thyroid was not enlarged. The chest was normal on physical examination. The heart was not enlarged to percussion. A grade 2 apical systolic murmur was present. The left groin was swollen and prominent, distended, tortuous veins were seen in this region. Although no thrill was palpable, a marked bruit was heard over this area. The left calf was considerably larger than the right.

The hemoglobin was 14 gm. The white blood count was 5,700 and the urine was normal. Chest films were reported as showing no abnormality.

Physiological studies: The oxygen content of left femoral artery and femoral vein bloods were identical. Cardiac catheterization revealed a normal right ventricular pressure. The cardiac output was 20,600 cc./min. or a cardiac index of 11,700 cc./min./M^2. The flow relationships are indicated in Figure 5. It should be pointed out that the cardiac output as determined by the direct Fick principle is less accurate at high flows. This is due to the fact that the arterio-mixed venous

oxygen difference is small and hence analytical and sampling errors become proportionally greater. The cardiac output in this case was markedly elevated. The systemic vascular resistance was reduced to 6.0 mm. Hg/L/min./M², (normal values are 23 to 33 mm. Hg/L/min./M²).

The patient was operated on and multiple arterio-venous fistulae involving the left iliac artery and vein were found. These were partially resected along with the left hypogastric artery and vein. Unfortunately no data as to the subsequent course is available.

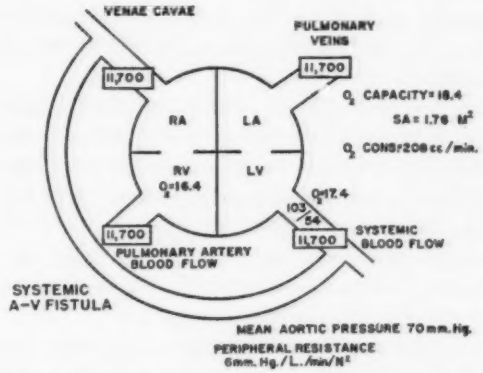

FIG. 5. DIAGRAM OF THE RESULTS OF CARDIAC CATHETERIZATION IN CASE 8 (J. K.) IN WHOM A SYSTEMIC ARTERIOVENOUS FISTULA WAS PRESENT

The total systemic resistance was reduced and, in contrast to the findings in the previous case of pulmonary arteriovenous fistula, the cardiac output was markedly increased.

Comment: The findings in this patient were typical of those reported in other cases of peripheral arteriovenous fistulae. No cyanosis or polycythemia were present. In contrast to the pulmonary resistance, the systemic vascular resistance is normally high. Hence, a systemic arteriovenous fistula will decrease the total systemic vascular resistance considerably and the arteriovenous fistula will transmit a large portion of the left ventricular output. The result is an increase in the cardiac output of major proportions which may lead to cardiac hypertrophy and even to congestive failure.

B. Pulmonary veins draining into the right auricle or its tributaries. In recent years a number of reports have appeared describing the clinical and pathological features of the anomalous drainage of pulmonary veins into the right auricle or its tributaries (7, 22, 23, 24, 25, 26, 27, and 28). Brody's analysis of 102 cases (25) has shown that the most frequent sites of anomalous drainage of pulmonary veins are the superior vena cava, the right auricle, the left innominate vein, the coronary sinus, and the portal vein. Dotter, Hardisty, and Steinberg (29), have described two cases in which a common right pulmonary vein drained into the inferior vena cava. The diagnosis was made by angiocardiography and, in one case, was substantiated by the finding of a high oxygen content of blood from the inferior vena cava on cardiac catheterization.

This section will deal with the results of physiological studies on eighteen patients in whom the presence of pulmonary veins draining into the right auricle or its tributaries was suspected. From the findings of cardiac catheterization there were six instances in which some of the pulmonary veins were believed to enter the right auricle, ten in which some pulmonary veins were believed to enter the superior or inferior vena cava, and two proven cases in which all of the pulmonary veins drained into the superior vena cava.

When the oxygen content of right auricular blood is found to be significantly higher (1.5 volumes per cent) than that of either venae cavae, one may suspect the presence of either an auricular septal defect or the anomalous drainage of pulmonary veins into the right auricle. More definitive evidence of the anomalous drainage of pulmonary veins into the right auricle is present if the catheter passes from what appears to be the right auricle directly into the lung field through one of these veins. This situation was present in the six cases summarized in Table III. However, four of these patients were believed to have, in addition, an auricular septal defect as indicated by angiocardiograms or by intubation of the left auricle. Although it is possible that the catheter had entered a normal pulmonary vein through an auricular defect, the fact that the catheter was seen to pass into the lung fields directly from the right border of the cardiac silhouette is strong evidence that the pulmonary vein entered the right auricle. It is of interest that angiocardiography revealed no anomalous

TABLE III

CASE NUMBER	NAME	AGE	SEX	OXYGEN CONTENT, VOLS. %							AURICULAR DEFECT DIAGNOSED BY	ANOMALOUS P.V. SEEN AT		OTHER ANOMALIES PRESENT
				SVC	IVC	Rt. aur.	Cath. pul. vein	Rt. vent.	Fem. art.	Rt. aur. minus cava		Angio	Surg.	
3	D. C.	8	M	16.5	16.1	18.9	23.6	19.7	18.4	2.6	Angio	No		Left SVC-LA, auricular defect
9	M. B.	8	F	12.2		15.7	31.0	11.4	15.7	3.5	Angio	No	No	Pul. stenosis, aur. defect
10	J. E.	7	F	17.8		19.6	29.6	20.8	21.2	1.8	?	No	No	Tetralogy, situs inversus with levocardia
11	C. S.	6	F	11.3		10.9	27.8	13.6	19.3	−0.4	Catheter angio	No		Pul. stenosis, aur. and vent. defect
12	S. R.	16	M	23.3		20.8	29.8		25.2	−2.5	?			Dextrocardia? Left SVC-CS-RA
13	C. Z.	9 wk.	F		6.8	9.6	*Clot*	10.7	9.5	2.8	Catheter			Aur. defect, transposition

Data obtained in six patients in whom some pulmonary veins were believed to drain into the right auricle.

pulmonary venous drainage in the four patients in whom this procedure was done. This may have been due to the presence of a low pulmonary blood flow, since three of the four patients had pulmonic stenosis. This anomaly was not present in the two cases described by Dotter,| Hardisty, and Steinberg (29) in which the anomalous pulmonary veins were visualized on angiocardiography. In the two patients subjected to operation, the region of the right auricle was not explored and hence no anomalous pulmonary veins were seen. Since all of these patients presented multiple congenital cardiac anomalies, the alteration in circulatory dynamics produced by the drainage of one or more pulmonary veins into the right auricle cannot be assessed.

Table IV summarizes the pertinent data obtained in ten patients in whom cardiac catheterization indicated drainage of pulmonary veins into the superior or inferior vena cava. Unfortunately, in many of the patients, both superior and inferior vena caval samples were not obtained. In patients in whom only a sample of blood from the superior vena cava was obtained, anomalous drainage of one or more pulmonary veins into the superior vena cava was suspected when the oxygen content of blood from the superior vena cava exceeded that of blood from the right auricle by at least 1.8 volumes per cent. This is illustrated by cases 14 to 19 inclusive (Table IV). In these patients the oxygen difference averaged 2.55 volumes per cent.

In case 20 (Table IV) there was clinical evidence of a patent ductus arteriosus. The oxygen content of blood from the superior vena cava was almost identical with that of right auricular blood. In addition to the oxygen gradient between right ventricular and the pulmonary artery blood, the systemic blood flow was significantly elevated to 5200 cc./min./M^2. At operation, in addition to a patent ductus arteriosus, the pulmonary vein from the left upper lobe was seen to empty into the superior vena cava. In retrospect, the apparent elevation of the calculated systemic blood flow was due to the unrecognized contamination of mixed venous with pulmonary vein blood. If an inferior vena caval blood sample had been obtained during cardiac catheterization, this error in diagnosis would have been avoided. In case 21 (Table IV) the difference in oxygen content of blood from the superior vena cava and that from the right auricle was only 0.6 volumes per cent. However, the catheter was seen to pass from the su-

TABLE IV

CASE NO.	NAME	AGE	SEX	OXYGEN CONTENT, VOLUMES PER CENT									ANOMALOUS P.V. SEEN AT		OTHER ANOMALIES PRESENT
				SVC	IVC	RA	RV	PA	Calc. P.V.	FA	% Sat.	SVC minus RA	Angio	Surg.	
14	G. W.	4	M	18.5		16.7	20.8		Cath. 29.6	19.2	62	1.8	No	No	Dextrocardia, rt. aortic arch, tetralogy, auricular defect
15	S. K.	12	M	19.0		15.4	14.5	17.1	24.7	17.6	69	3.6			Pul. stenosis, patent ductus, rt. aortic arch
16	T. H.	7	M	14.5		12.4	12.8	13.9	19.2	14.9	75	2.1	No		Pulmonic stenosis
17	J. H.	7	F	22.3		18.7	20.6		26.5	Aorta 20.7	71	3.6			Transposition, vent. defect, dextrocardia
18	R. A.	3	M	17.0		14.6	16.0		27.8	18.9	65	2.4	No	No	Tetralogy
19	F. M.	17	F	16.7		14.9	15.2	15.2	16.6	16.6	97	1.8			None
20	L. W.	3	M	11.7		11.9	11.7	13.1	14.8	14.8	97	−0.2		Yes	Patent ductus
21	H. A.	6	M	14.3		13.7			Cath. 17.1	Aorta 16.5	89	0.6			L. SVC-CS-RA, Eisenmenger's or truncus
22	J. H.	7	M	13.1	18.9	17.9	21.3		25.1	Aorta 20.0	77	1.0			Transposition, vent. defect, rt. aortic arch
23	V. P.	11	F	16.6	13.3	14.9	14.8		26.7	17.8	64	1.7	No	No	Tetralogy, L. SVC-CS-RA

Data obained from ten patients in whom one or more pulmonary veins were believed to drain into one of the venae cavae.

perior vena cava directly into the left lung field. Case 22 (Table IV) is believed to illustrate an example of the drainage of one or more pulmonary veins into the inferior vena cava. Although the oxygen content of inferior vena caval blood was only 1.0 volumes per cent higher than that of the right auricle, it was 5.8 volumes per cent higher than that of blood from the superior vena cava, strongly indicating the drainage of a pulmonary vein into the inferior vena cava. Similarly, in case 23 (Table IV) the oxygen content of the superior vena caval blood was only 1.7 volumes per cent higher than that of the right auricle, whereas it was 3.3 volumes per cent higher than that of the inferior vena cava. Normally the oxygen content of blood in the superior vena cava is somewhat lower than that in the inferior vena cava. Therefore, the findings in case 23 are strong evidence of the anomalous drainage of pulmonary veins into the superior vena cava.

In nine of these ten patients there were other congenital cardiac defects, so that the alteration of circulatory dynamics produced by the anomalous drainage of pulmonary veins alone cannot be assessed. It is noteworthy, however, that two patients (#17 and 22) had transposition of the great vessels. Under this circumstance, the drainage of pulmonary veins into the right side of the heart constitutes a compensatory mechanism by allowing oxygenated blood to enter the systemic circulation in addition to that which is shunted from left to right in the heart. The blood flows and shunts could not be calculated in these patients, but their peripheral arterial oxygen saturations were 71 and 77 per cent respectively, figures which are unusually high for cases of transposition of the great vessels. Clinically the two patients under discussion were not thought to be sufficiently incapacitated to warrant surgical treatment. These considerations may be taken as further evidence that the transposition of the great vessels in these patients had been partially corrected by the compensatory drainage of pulmonary venous blood into the right side of the heart.

Case 19 (Table IV) is the one patient of this group in whom the only congenital malformation present was that of anomalous drainage of one or more pulmonary veins into the superior vena cava. Blood obtained from the superior vena cava was 98 per cent saturated with oxygen and the saturation of that from the pulmonary artery was 89 per cent. Unfortunately, no inferior vena cava sample was obtained

and therefore, the oxygen content of mixed venous blood was not known. For this reason, the systemic and effective pulmonary blood flows could not be calculated. The pulmonary artery blood flow in this patient was 8320 cc./min./M^2. This marked elevation in pulmonary blood flow was not associated with an increase in the pulmonary resistance since the pulmonary artery pressure was normal (16 mm. Hg systolic and 9 mm. Hg diastolic). It is apparent that as the volume of pulmonary vein blood entering the superior vena cava increases, a point is reached where the difference in oxygen content of blood from the superior vena cava and the right auricle decreases. Therefore, in cases in which there is a large volume of pulmonary venous flow entering the superior vena cava, a knowledge of the oxygen content of inferior vena cava blood is of great importance in establishing a diagnosis.

Two patients have been studied in this laboratory in whom all of the pulmonary veins drained into the superior vena cava or a tributary thereof. In both patients the only other associated anomaly was patency of the foramen ovale. Both patients died and postmortem examinations were done.

Case 24. K. F. This four year old girl was referred to the hospital by Dr. Robert F. Ziegler of Detroit, with a diagnosis of pulmonary veins draining into the superior vena cava.[4] The clinical aspects of this case are to be published by Dr. Ziegler (30); hence, only the results of cardiac catheterization will be reported here.

The findings are summarized in Table V. The oxygen content of blood taken from the dilated pulsating portion of the superior vena cava was 3.9 volumes per cent higher than that of blood taken from very high in the superior vena cava. It will be noted that blood samples from the right auricle, right ventricle, and femoral artery had almost identical oxygen contents. These findings led to the conclusion that all the pulmonary venous drainage was into the right side of the heart. If some of the pulmonary veins had emptied into the left auricle, the oxygen content of femoral artery blood would have exceeded that of blood from the right ventricle. Although no patient with such an anom-

[4] Dr. Ziegler had studied this patient both clinically and by cardiac catheterization. He has kindly consented to the publication of the data obtained in this laboratory which substantiated his findings.

TABLE V

CASE NO.	NAME	AGE	SEX	SURFACE AREA (M^2)	O_2 CONSUMP. CC./MIN.	OXYGEN CONTENT VOLS. % PRESSURE (MM. Hg) BELOW									BLOOD FLOW, CC./MIN./M^2			SHUNT, CC./MIN./M^2		MEAN P. A. PRESSURE, MM. Hg		PUL. RESIST. MM./L./MIN./M^2
						High SVC	SVC	Rt. aur.	Rt vent.	Pul. art.	Pul. vein (calc.)	Fem. art.	O_2 cap.	% Sat.	Pul.	Eff. pul.	Syst.	L-R	R-L			
24	K. F.	4	F	0.58	80	11.8	15.7	16.5 22/18	16.6 126/6		17.6	16.5	18.4	90	13,930	2360	2910	11,570	550	89	assumed	6.4
25	J. G.	2	M	0.50	60	10.7 IVC 10.1	14.0	14.7	13.4 78/2	13.8	16.2	13.6	16.9	81	4,960	2060	3720	2,900	1660	59	assumed	12

Data obtained from cardiac catheterization in two patients in whom all of the pulmonary veins drained into the superior vena cava.

aly had ever been subjected to cardiac catheterization, Taussig (7), had previously pointed out that in this malformation the oxygen content of blood in all cardiac chambers should be identical. The pulmonary blood flow of this patient was significantly elevated (13,930 cc./min./M²).

As may be seen in Figure 6 the large total left to right shunt as calculated by equation 5, represents only that portion of the pulmonary venous return to the right auricle which then enters the right ventricle. The remainder of the pulmonary blood flow passes into the left auricle

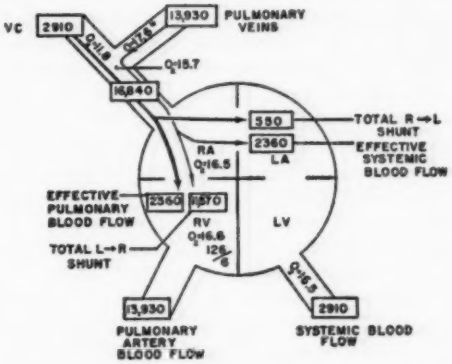

FIG. 6. CIRCULATORY DIAGRAM OF THE FINDINGS IN CASE 24 (K. F.)

All of the pulmonary veins drained into the superior vena cava and a patent foramen ovale was present. The oxygen content of blood in all cardiac chambers was identical. The pulmonary blood flow was markedly increased.

through the patent foramen ovale. The right ventricular systolic pressure was elevated to 126 mm. Hg. The pulmonary artery was not entered. If, however, one assumes a pulmonary arterial pressure of 126 mm. Hg systolic and a correspondingly elevated diastolic pressure, the pulmonary resistance would be slightly above normal. It was concluded that all of the pulmonary veins drained into the superior vena cava and that the large volume of blood flow through the superior vena cava accounted for the venous hum which could be heard in the second right intercostal space. Despite the considerable pulmonary hypertension, the pulmonary vascular resistance was not markedly elevated.

The patient died on the second day following thoracotomy for the attempted surgical relief of her condition. Autopsy revealed all of the pulmonary veins joining into a common trunk and draining into the superior vena cava. The foramen ovale was widely patent, the left atrium and ventricle were very small, and there was marked hypertrophy of the right ventricle. The pulmonary arterioles appeared normal on microscopic examination.

Case 25. J. G. This two year old boy entered the hospital with clinical and roentgenological findings which were almost identical with those of the previous case. Since the age of six months the patient had experienced three episodes of bronchopneumonia which necessitated hospitalization. There were also several bouts of tonsillitis and of otitis media. At the time of his second hospitalization, at the age of nine months, digitalis was given because of the findings of cyanosis, gallop rhythm, and cardiac enlargement. No cyanosis had been noted subsequent to this hospitalization. There had been no squatting or dyspnea on exertion.

Physical examination: The patient was well developed and nourished. Cyanosis was noted only when he cried. There was slight bulging of the precordium. The blood pressure was 106/70 mm. Hg. The apex impulse was 1 cm. outside the midclavicular line. A harsh systolic murmur could be heard over the entire precordium which was maximal in the fourth intercostal space to the left of the sternum. No diastolic murmur was heard. The liver was enlarged to 1 cm. below the costal margin, but did not pulsate. There was no clubbing or edema.

The red blood count was 4.03 million and the hemoglobin 13.0 grams per cent. Abnormal features of the electrocardiogram were broad notched P waves, a prolonged P-R interval, right axis deviation, and evidence of right ventricular hypertrophy. Fluoroscopy of the heart revealed definite right ventricular and marked right auricular enlargement. The conus of the right ventricle and the pulmonary arteries were prominent and the lung fields were very vascular. The region of the superior vena cava was enlarged and pulsated.

Physiological studies: The results of cardiac catheterization are summarized in Table V. The oxygen content of blood from the dilated portion of the superior vena cava was 3.6 volumes per cent higher than the average of that obtained from the inferior vena cava, and that obtained from the left innominate vein. This indicated the entrance of highly oxygenated blood into the superior vena cava. The oxygen content of blood from the right ventricle, pulmonary artery, and the femoral artery were almost identical (Fig. 7). This combination of findings again led to the conclusion that all of the pulmonary veins drained into the superior vena cava. The right ventricular systolic pressure was elevated to 78 mm. Hg. If one assumes a pulmonary artery systolic pressure of 78 mm. Hg and a correspondingly elevated diastolic pressure, the pulmonary resistance would be definitely increased. The flow rela-

tionships are illustrated in Figure 7. There is an elevated pulmonary blood flow. In contrast to the previous patient, the oxygen saturation of peripheral arterial blood was reduced to 81 per cent. This is due to the fact that the ratio of the volume of oxygenated blood to venous blood emptying into the right auricle is lower than in the previous patient. It was concluded that this patient had an anomalous drainage of all of the pulmonary veins into the superior vena cava, that an auricular septal defect or patent foramen ovale must be present, and that the pulmonary resistance was increased. It was of particular interest

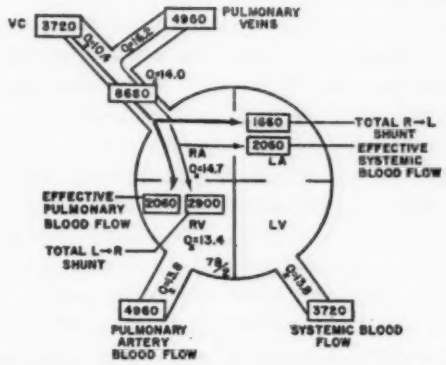

FIG. 7. CIRCULATORY DIAGRAM OF THE FINDINGS IN CASE 25 (J. G.) IN WHOM ALL OF THE PULMONARY VEINS DRAINED INTO THE LEFT INNOMINATE VEIN AND A PATENT FORAMEN OVALE WAS PRESENT

As in the previous patient, there was very little difference in oxygen contents of blood from the various cardiac chambers.

that this patient had developed a definite increase in pulmonary resistance at the age of two. Following surgery, the patient developed severe and uncontrollable hyperpyrexia and died several hours later.

Autopsy findings: On postmortem examination, all of the pulmonary veins were seen to join into a common trunk which ascended to join the left innominate vein. This common pulmonary vein was not in close relationship to the tip of the coronary sinus and therefore it is doubtful that it represented a left superior vena cava. The right atrium was markedly enlarged. A widely patent foramen ovale led to a small left atrium into which no pulmonary veins entered. The right ven-

tricle was markedly hypertrophied while the left ventricle was small. There was no pulmonary edema. The microscopic sections of pulmonary tissue revealed normal pulmonary arterioles.

Comment: Six cases are presented in which the results of cardiac catheterization indicated the probable presence of pulmonary veins draining into the right auricle. This diagnosis was suspected when the oxygen content of blood from the right auricle was significantly higher than that from the venae cavae and, in addition, the catheter was seen to pass from what was believed to be the right auricle directly into the lung fields.

The findings obtained by cardiac catheterization are described in ten patients in whom one or more pulmonary veins were believed to enter the superior or the inferior vena cava. The importance of obtaining samples from both the superior and inferior vena cava in evaluating these anomalies is stressed. In two of the patients described, transposition of the great vessels was also present. Under this circumstance, the anomalous pulmonary venous drainage into the right side of the heart constituted a compensatory anomaly which benefited the patients by increasing the amount of left to right shunt, thereby increasing the supply of oxygenated blood to the systemic circulation. In one patient, the anomalous drainage of some pulmonary veins into the superior vena cava was present as the sole cardiac anomaly. This patient had a greatly elevated pulmonary blood flow with no evidence of increased pulmonary resistance.

Two patients are described in whom all of the pulmonary venous drainage was into the superior vena cava. The only other cardiac anomaly was patency of the foramen ovale. From the diagnostic standpoint, the important features are the evidence of oxygenated blood entering the superior vena cava and the finding of comparable blood oxygen contents in all chambers of the heart, the pulmonary artery, and the systemic arteries. From the results of cardiac catheterization alone, this anomaly can be differentiated from a systemic arteriovenous fistula only by the peripheral arterial unsaturation resulting from the intracardiac shunt. The degree of unsaturation depends on the ratio of the volume of oxygenated to mixed venous blood entering the right auricle. Patient number 24 had only a slight increase in pulmonary resistance whereas the pulmonary resistance in the younger patient was significantly elevated.

III. Conditions constituting no shunt

Persistent left superior vena cava. The persistence of a left superior vena cava has been reported by several authors (31, 32) and its embryological development from the primitive left precardinal vein has been described. Since, in the embryo, the left precardinal vein drains into the left duct of Cuvier and the latter structure ultimately forms the coronary sinus, it follows that a persistent left superior vena cava should drain into the coronary sinus, and thence, into the right auricle. When such is the case, the systemic venous blood, carried by the left vena cava, enters the right auricle and no abnormality of hemodynamics results.

In eleven of the patients studied in this laboratory a persistent left superior vena cava was found (cases 12, 21, 22, and 26 to 33). In all cases the anomalous vena cava was thought to enter the right auricle through the coronary sinus. In only one patient, who had acquired aortic valvular disease, was the persistent left superior vena cava the only congenital cardiac abnormality. In the remaining ten cases, other congenital defects were present including coarctation of the aorta (#32), isolated septal defects (#31) the Tetralogy of Fallot (#22, 26, 27, 29), transposition of the great vessels (#28), and Eisenmenger's complex (#21). In two of the patients (#21, 23) there was anomalous drainage of one or more pulmonary veins into the left superior vena cava. In three patients the left superior vena cava was seen at operation or by angiocardiograms done from the left side. In three patients (#28, 30, 31), proof of the drainage of the left superior vena cava through the coronary sinus was obtained by sampling blood from the region of the coronary sinus. The oxygen content of these samples averaged 6.8 volumes per cent lower than that of the blood taken from higher in the left superior vena cava or from the right superior vena cava. When a left superior vena cava is present and the catheter is introduced from the left arm, it takes a characteristic course as illustrated in Figure 8. In the antero-posterior view the catheter approaches the left cardiac border in the region of the pulmonary conus traversing the cardiac silhouette obliquely downward and to the right, entering the right auricle just superior to the origin of the inferior vena cava. In the lateral projection, the catheter may be seen along the posterior margin of the cardiac shadow. From the coronary sinus ostium the catheter may enter the right superior vena cava, or, by

looping in a clockwise direction, may enter the right ventricle. This was done in nine of the eleven patients presented here. It is very difficult, however, to direct the catheter from the right ventricle into the pulmonary artery. It was possible to enter the pulmonary artery in only two patients. When it is of particular importance to enter the pulmonary artery, the patient may be recatheterized using a right arm vein.

In summary, the occurrence of a persistent left superior vena cava has no physiological importance since it constitutes no shunt. It is

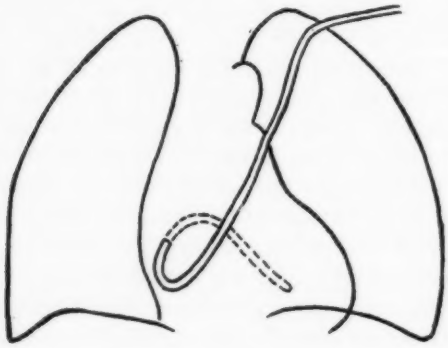

FIG. 8. DRAWING OF THE FLUOROSCOPIC APPEARANCE OF A CATHETER ENTERING THE RIGHT AURICLE THROUGH A LEFT SUPERIOR VENA CAVA AND THE CORONARY SINUS

The dotted lines illustrate the clockwise loop which the catheter must make to enter the right ventricle.

occasionally the site of anomalous pulmonary venous drainage and may make catheterization of the pulmonary artery difficult. Because of the extremely low oxygen content of coronary sinus blood, samples collected from the region of the coronary sinus are not representitive of mixed venous blood.

SUMMARY

Results of physiological tests in thirty-four patients with anomalies of the venous return to the heart have been presented. Those with anomalies resulting in a right to left shunt included four patients in

whom a superior vena cava drained into the left auricle and four patients with pulmonary arteriovenous fistulae. Those with anomalies resulting in a left to right shunt included one patient with a systemic arteriovenous fistula and eighteen patients in whom pulmonary veins drained into the right auricle or a tributary thereof. In eleven patients there was a persistent left superior vena cava.

Formulae used in the calculation of the volume of various flows and shunts were restated. The assumption that pulmonary vein blood was 96 per cent saturated with oxygen was substantiated by the findings in twenty-four patients in whom pulmonary vein blood had been sampled. The calculated vascular resistance was corrected for variations in blood viscosity due to variations in the hematocrit.

In the patients in whom a superior vena cava drained into the left auricle the malformation resulted in a right to left shunt and peripheral arterial unsaturation.

In the patients with pulmonary arteriovenous fistulae an average of 62.5 per cent of the right ventricular output coursed through the fistulae. Three of the patients studied had a normal pulmonary vascular resistance, a normal cardiac output, and no cardiac enlargement. In the fourth patient the pulmonary vascular resistance was lower, the cardiac output was elevated, and cardiac enlargement was present. The vascular resistance of the lung exclusive of the fistula was elevated in all four patients, averaging 9.3 mm. Hg/L./min./M^2. The resistance of the arteriovenous fistulae averaged 5.8 mm. Hg/L./min./M^2.

The cardiac output in the patient with a systemic arteriovenous fistula was markedly elevated. The reasons for the difference in hemodynamics between the two types of arteriovenous communication were discussed.

Of the eighteen patients with anomalous drainage of pulmonary veins, the drainage was into the right auricle in six instances and into one of the venae cavae in ten. In two patients of the latter group transposition of the great vessels was present and was partially corrected by the anomalous pulmonary venous drainage.

The physiological studies in two patients in whom all of the pulmonary veins drained into the superior vena cava were presented. The characteristic findings in this anomaly were discussed. This malformation resulted in a marked increase in the pulmonary blood flow.

In eleven patients a persistent left superior vena cava drained into the right auricle through the coronary sinus. The malformation resulted in no change in the hemodynamics, but made intubation of the pulmonary artery difficult.

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RENAL HEMODYNAMICS IN CONGENITAL CYANOTIC HEART DISEASE

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The physiologic studies of Bing and his co-workers (1, 2) in patients with congenital cyanotic heart disease have yielded considerable information relative to the mechanisms of adaptation to anoxia in cyanotic patients. These studies have shown that the systemic blood flow varies considerably in such patients depending on the magnitude of the total right to left shunt. Furthermore, it also has been shown that the right to left shunt is responsible for the considerable decrease in the mean oxygen tension of capillary blood. As a result of low oxygen tension the oxygen-carrying capacity of the blood is increased by an increase in the number of red cells. Since it is possible to study accurately the dynamics of the kidney by means of methods developed by Homer Smith and his associates it seemed of interest to investigate the possible effects of anoxemia and polycythemia on the renal dynamics in patients with congenital cyanotic heart disease.

These investigations were carried out on 19 patients with congenital cyanotic heart disease who were admitted to the surgical service of the Johns Hopkins Hospital for study prior to surgical correction of their cardiac lesion. All patients had diminution in effective pulmonary blood flow (1) and evidence of a right to left shunt. Their ages ranged from 5 to 45 years. There were 11 males and 8 females in the group studied. Simultaneous measurements of the renal clearances of para-aminohippuric acid (PAH) and inulin were made in all patients following the general techniques outlined by Homer Smith and his associates (3, 4). In the last 9 of the 19 patients the clearances were combined with catheterization of the right renal vein, permitting the determination of renal extraction of oxygen and PAH.

METHODS

All tests were carried out in fasting patients who had received no sedation. In the first 10 patients the clearances were done in the morning under basal conditions with the exception that tap water was given freely before and during the clearance.

In the second group of 9 patients in whom renal vein catheterization was employed the procedures were done in the afternoon. All the latter patients received nothing by mouth after breakfast excepting tap water, and each was given an intramuscular injection of penicillin prior to venous catheterization. Diagnostic cardiac catheterization was carried out in each of these patients by R. J. Bing and his associates. After completing the intracardiac manipulations the catheter was passed into the right renal vein. Standard clearance techniques were then instituted.

Inulin clearance was used to measure the glomerular filtration rate. The clearance of PAH was used for the determination of effective renal plasma flow and the maximal functional capacity of the tubular excretory mechanism.

Urine was obtained from each patient by an indwelling catheter, usually of the Foley type. A control urine specimen was collected in each case for determination of blank substances. After obtaining a blood sample from a peripheral vein for determination of plasma blank, an intravenous infusion of normal saline to which had been added PAH and inulin was commenced. Immediately after starting the infusion, a priming dose of PAH and inulin was given. Priming and sustaining dosages were calculated to yield constant plasma concentrations of 15 to 20 mg. per cent of inulin for glomerular filtration rate and 2 to 3 mg. per cent of PAH for effective renal plasma flow. In 7 patients, after completing the measurements of renal plasma flow, the maximal excretory capacity of the tubules for PAH (Tm_{pah}) was measured by Homer Smith's technique (4). Dosages of PAH for this determination were given to maintain a plasma concentration of 60 mg. per cent.

A constant infusion rate of 40 drops per minute was maintained throughout each clearance. A "mixing" period of 15 to 20 minutes after the priming injection was allowed for equilibrium to be reached.

Urine collected during this period was discarded. Three to six urine collection periods were used for each patient. The collection periods were usually 10 minutes in length except when low urine flow required extension to 15 to 20 minutes. At the end of each period the catheterized bladder was emptied by air injection and manual pressure.

Two blood samples from a peripheral vessel were drawn for each three urine collections—usually at the midpoints of the first and third periods. In the last 9 patients blood specimens were drawn simultaneously from the catheterized renal vein and the peripheral vessel.

Heparin was used as the anticoagulant. Metycaine was employed for local anesthesia in the cases of venous catheterization since it does not interfere with the determination of PAH as does procaine. Wintrobe hematocrits were obtained in all patients. Blood urea and non-protein nitrogen levels were determined by the method of Gentzkow (5). PAH was determined by the method of Smith et al (3). Inulin was determined by the method of Harrison as modified by Goldring and Chasis (6), except that the inulin standards were yeasted as well as the plasma and diluted urine specimens and proteins were precipitated by Somogyi's method (7).

Plasma PAH and inulin levels and urine inulin levels were corrected for blank substances. In all cases the urine PAH blank was so minute that it was ignored.[2] The plasma levels were plotted on semilogarithmic paper, and the levels used in clearance calculations were those obtained from the curve at a time two minutes prior to the midpoint of the urine collection period.

Calculations of glomerular filtration rate and renal plasma flow are based on the formula UV/P for inulin and for PAH respectively. The "corrected" renal plasma flows in the 9 patients with renal vein catheterization are calculated from the formula $UV/P - P_{rv}$, where P_{rv} is the PAH concentration in renal vein plasma.

Renal blood flow is calculated from the formula:

$$\text{Renal Blood Flow (cc./min./m.}^2\text{)} = \text{Renal Plasma Flow (cc./min./m.}^2\text{)} \times \frac{100}{100 - \text{Hematocrit}}$$

[2] In 17 patients the PAH plasma blank ranged from 0 to 0.35 mg. per cent and averaged 0.10 mg. per cent. Unexplained high plasma PAH blanks of 1.22 mg. per cent and 1.34 mg. per cent were found in 2 patients who had received neither procaine nor sulfonamides. The urine PAH blanks averaged less than 0.5 mg. per

Filtration fraction is the ratio between glomerular filtration rate and renal plasma flow (Clearance of inulin/Clearance of PAH). It represents the percentage of water filtered from plasma by the glomeruli (8).

Tm_{pah}, the maximal quantity of PAH which can be excreted by the tubules, is calculated from the formula (9):

$$Tm_{pah}\ (mg./min.) = U_{pah}\ V - \text{Clearance of inulin} \times P_{pah} \times 0.83$$

where U_{pah} is the concentration of PAH in urine in mg./cc.

V is urine volume in cc./min.

P_{pah} is the concentration of PAH in plasma in mg./cc.

0.83 is a factor which takes into account the fact that some PAH is bound to plasma protein.

The percentage of PAH extracted from plasma by the kidney is determined from the formula:

$$\text{Per cent Extraction PAH} = \frac{P - P_{rv}}{P} \times 100$$

where P is the peripheral plasma concentration of PAH in mg./cc.

P_{rv} is the renal vein plasma concentration of PAH in mg./cc.

The renal oxygen consumption may be calculated from the formula:

$$\text{Renal } O_2 \text{ Consumption (cc./min.)} = \frac{\text{Arterial } O_2 \text{ content (vol. per cent)} - \text{Renal Vein } O_2 \text{ content (vol. per cent)}}{100} \times \text{Renal blood flow (cc./min.)}$$

Oxygen levels were measured by the manometric method of Van Slyke and Neill (10).

Measurements of systemic flow, or the volume of blood perfusing the systemic capillaries per minute, is determined by application of the Fick principle according to the formula (11):

$$\text{Systemic Flow (cc./min./m.}^2\text{)} = \frac{O_2 \text{ intake (cc./min.)}}{O_2 \text{ content of arterial blood (vol. per cent)} - O_2 \text{ content of mixed venous blood (vol. per cent)}} \times 100$$

cent. The inulin plasma blanks ranged from 0.2 mg. per cent to 4.5 mg. per cent and averaged 1.03 mg. per cent. The inulin urine blanks averaged 7 mg. per cent.

RESULTS

Table 1 shows a summary of the observations in 19 patients with congenital cyanotic heart disease. The data for renal blood flow, renal plasma flow, glomerular filtration rate and systemic flow are corrected to a surface area of 1.73 square meters for purposes of comparison.

In the 9 patients in whom renal vein catheterization was used (Table 1—Group 2) extraction ratios for PAH were determined. In Table 1 measurements of renal plasma flow, renal blood flow and filtration fraction are tabulated for these 9 patients with and without correction for extraction ratio. We have elected to use uncorrected values from the entire group of 19 patients for comparison with previously reported normal standards.

The glomerular filtration rate as measured by the clearance of inulin in these cyanotic patients ranged between 53 cc. and 176 cc. per minute per 1.73 square meters. The mean filtration rate for Group 1 was 114 cc. and for Group 2 it was 106 cc. The average for all 19 patients was 110 cc. Although this average is slightly less than the mean standard normal filtration rate of 124 cc. (Figure 1) the distribution of the data falls within the normal range.

The effective renal plasma flow in the 19 cyanotic patients averaged 379 cc. per minute per 1.73 square meters (Figure 1), with a range of 150 cc. to 666 cc. The patients in Group 1 had slightly higher plasma flows (average 402 cc.) than those in Group 2 (average 353 cc.). All the observed data with a single exception were below the mean normal standard for renal plasma flow of 646 cc. per minute (Table 1). Ninety per cent of the data fell below the range which statistically contains 95 per cent of normal values (12). The renal plasma flow in the cyanotic patients is, thus, markedly depressed.

The filtration fraction (Clearance of Inulin/Clearance of PAH) in the 19 cyanotic subjects averaged 0.31 as compared with the normal standard of 0.16 (Figure 1). In Group 1 the average was 0.29 and in Group 2 it was 0.33. The filtration fraction in the patients under study ranged from 0.20 to 0.55,[3] all values lying above the normal standard

[3] The extremely high filtration fraction of 0.55 f[illegible] in patient Number 16 is so high as to be of questionable validity. If this val[illegible] excluded the mean for filtration fraction of the remaining 18 patients is 0.[illegible]

TABLE 1

Summary of observations in 19 patients with congenital cyanotic heart disease

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NO.	SUBJ.	AGE	SEX	SURFACE AREA	HEMATOCRIT		PAH EXTRACTED BY KIDNEY	GLOMERULAR FILTRATION RATE	RENAL PLASMA FLOW		RENAL BLOOD FLOW		FILTRATION FRACTION		T_{max} PAH	SYSTEMIC FLOW PER 1.73 M^2	RENAL FRACTION OF SYSTEMIC FLOW	RENAL O_2 ARTERIAL VENOUS DIFF.	RENAL OXYGEN CONSUMPTION	MILLIGRAM PER CENT		OXYGEN SATURATION OF RENAL VEIN BLOOD
					Peripheral	Renal vein			Uncor. for P_{rv}	Cor. for P_{rv}	Uncor. for P_{rv}	Cor. for P_{rv}	Uncor. for P_{rv}	Cor. for P_{rv}						BUN	NPN	
Group 1																						
		yr.		M^2			%											vol. %				%
1	D. P.	5	F	0.46	77.1	—	—	176	666	—	2308	—	0.26	—	—	—	—	—	—	—	—	—
2	S. R.	12	M	1.08	88.0	—	—	153	379	—	3105	—	0.41	—	67	—	—	—	—	—	—	—
3	E. M.	12	M	1.09	87.8	—	—	120	380	—	3116	—	0.31	—	62	—	—	—	—	15.8	—	—
4	H. P.	32	F	1.43	73.1	—	—	65	200	—	742	—	0.33	—	65	4000	18.6	—	—	11.5	—	—
5	K. S.	22	F	1.68	63.8	—	—	124	391	—	1079	—	0.32	—	85	4930	21.9	—	—	9.8	—	—
6	J. S.	22	M	1.51	77.3	—	—	91	460	—	2028	—	0.20	—	72	—	—	—	—	14.9	—	—
7	M. F.	16	M	1.27	83.3	—	—	110	409	—	2455	—	0.27	—	84	5200	47.3	—	—	15.6	—	—
8	R. V.	11	M	1.04	59.8	—	—	111	366	—	913	—	0.31	—	67	—	—	—	—	10.7	—	—
9	S. X.	15	M	1.16	84.0	—	—	81	342	—	2138	—	0.24	—	—	4240	50.5	—	—	18.0	—	—
10	N. N.	13	F	1.29	78.9	—	—	109	430	—	2043	—	0.25	—	—	—	—	—	—	8.4	17.3	--
Group 2																						
11	G. R.	29	M	1.58	72.0	—	84.0	99	499	592	1783	2114	0.20	0.17	—	2960	60.3	1.5	15.5	16.4	—	74.0
12	G. N.	12	M	1.39	79.7	78.2	87.0	53	150	174	741	799	0.35	0.31	—	4050	18.3	0.7	3.0	11.4	19.5	63.9
13	F. T.	45	M	1.66	81.5	81.2	75.5	71	203	269	1091	1419	0.35	0.27	—	4960	22.1	—	—	22.8	42.0	—
14	W. K.	18	M	1.73	73.1	72.8	96.2	105	425	446	1582	1637	0.25	0.24	—	2680	59.0	1.7	15.6	15.0	27.0	79.6
15	J. C.	11	F	0.99	50.6	(49.6)	(37.3)	112	294	(789)	594	(1568)	0.38	(0.15)	—	2940	20.2	(2.6)	(8.9)	12.0	19.5	(69.3)
16	S. D.	14	F	1.44	66.9	(66.7)	(49.5)	96	177	(358)	533	(1075)	0.55	(0.27)	—	—	—	(0.8)	(2.5)	9.0	16.5	(69.3)
17	R. H.	20	M	1.65	71.7	71.6	89.4	172	505	568	1783	2001	0.35	0.31	—	—	—	3.4	35.0	13.8	24.0	75.0
18	V. T.	25	F	1.30	71.0	70.5	87.1	124	538	615	1823	2033	0.23	0.20	—	5330	34.2	1.5	15.8	8.4	21.0	72.6
19	A. R.	22	F	1.73	60.5	61.6	90.6	120	385	425	977	1110	0.31	0.28	—	3220	30.3	1.0	5.7	9.6	28.5	75.9
Average subjects 1–10 (group 1)...		16.0	—	1.20	76.7	—	—	114	402	—	1997	—	0.29	—	71.7	4593	34.6	—	—	—	—	—
Average subjects 11–19 (group 2)..		21.6	—	1.50	69.7	69.0	77.4	106	353	471	1211	1528	0.33	0.24	—	3734	34.9	1.7	12.9	—	—	72.5
Average subjects 1–19.....		18.7	—	1.34	73.4	—	—	110	379	—	1625	—	0.31	—	—	4046	34.8	—	—	—	—	—
Average normal....		—	—	1.73	44.5 (*13*)	—	88 (*14*)	124 (*12*)	646 (*12*)	—	1164 (*)	—	0.16 (*12*)	—	78 (*12*)	5398 (*15*)	21.5 (*)	2.4 (*14*)	16.2 (*)	—	—	—

* See footnotes in text.

plus twice the standard deviation as reported by Smith and his associates (12).

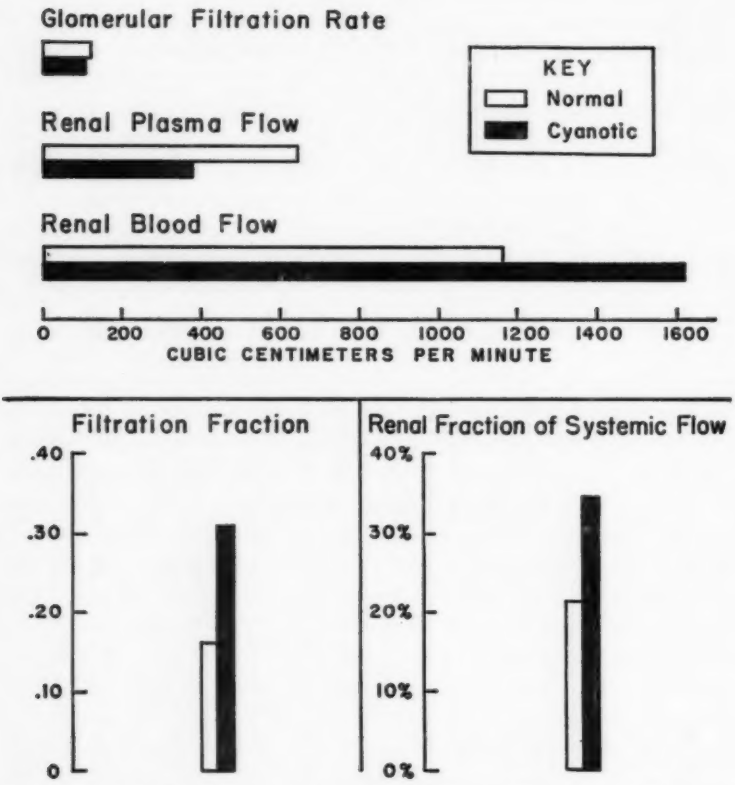

FIG. 1. GRAPHIC COMPARISON OF AVERAGES OF RENAL DATA IN 19 CYANOTIC PATIENTS WITH NORMAL STANDARDS

Renal blood flow is calculated from the renal plasma flow by use of the uncorrected hematocrit. The renal blood flow in these 19 patients averaged 1625 cc. per minute per 1.73 square meters. The minimum value observed was 533 cc. while the maximum was 3150 cc. The wide

variation in these data reflects the spread of the observed values for renal plasma flow and hematocrit. In Group 1 the average renal blood flow was 1997 cc. while in Group 2 it was 1212 cc. The renal plasma flows and the hematocrits were higher in the patients of Group 1. In Figure 1 the average value for renal blood flow in the 19 cyanotic patients is compared with the normal standard.[4] Elevation of the calculated renal blood flow in these patients with low renal plasma flow is obviously a function of the excessively high hematocrits.

The average uncorrected hematocrit of peripheral venous blood in the 19 cyanotic patients was 73.4 per cent as compared to the normal standard (13) of 44.5 per cent. In the patients of Group 1 hematocrits averaged 76.7 per cent while in those of Group 2 the average was 69.7 per cent. There was no significant difference between peripheral and renal vein hematocrits in Group 2.

In the 9 patients in whom renal vein catheterization was attempted accurate catheterization was achieved in 7 cases. The extraction of PAH by the kidney in these 7 patients ranged from 75.5 per cent to 96.2 per cent and averaged 87.0 per cent. This value is essentially the same as that found by Warren, Brannon and Merrill (14) in normal subjects. In 2 of our patients (Table 1) renal vein catheterization was questionable. In one patient (J. C.—Number 15 in Table 1) the extraction of PAH was 37.3 per cent and the position of the venous catheter by fluoroscopy was never entirely satisfactory. In the other patient (S. D.—Number 16 in Table 1) the position of the catheter by fluoroscopy was satisfactory, the renal arterio-venous oxygen difference was 0.8 vol. per cent, but the extraction of PAH was only 49.5 per cent. If it is assumed that the catheter were in the renal vein in this patient then the values for renal plasma and blood flow would be nearly doubled and the filtration fraction reduced from 0.55 to 0.27.

[4] The normal standard for renal blood flow is calculated by using the average normal renal plasma flow of 646 cc. per minute (12) and an average normal hematocrit of 44.5 (13) in the formula:

$$\text{Renal Blood Flow} = \text{RPF} \times \frac{100}{100 - \text{Hematocrit}}$$

$$\therefore \text{Renal Blood Flow} = 646 \times \frac{100}{100 - 44.5} = 1164 \text{ cc.}$$

The maximal excretory capacity of the renal tubules (Tm_{pah}), was determined in 7 patients. The observed values ranged from 62 to 85 mg. per minute and averaged 72 mg. per minute. These values fall within the normal range as reported by Smith, et al (12).

Measurement of systemic blood flow was made in 11 of these 19 cyanotic patients by R. J. Bing and his associates. Systemic flow ranged from 2680 cc. to 5330 cc. per minute per 1.73 square meters. The average systemic flow in 4 patients in Group 1 was 4593 cc. while the average in 7 patients in Group 2 was 3734 cc. The overall average value was 4046 cc. per 1.73 square meters. Cournand's mean standard for systemic flow in normal subjects using right heart catheterization is reported (15) as 3.12 liters per minute per square meter. Corrected to 1.73 square meters this standard becomes 5398 cc. per minute. The values for systemic flow in the 11 cyanotic subjects under study all lie below this standard. It is probable that the reduction in systemic flow in these cases results from anatomical variations of the cardiac malformation (1).

An attempt has been made to calculate the percentage of the systemic flow perfusing the kidneys (renal fraction) in these 11 cyanotic individuals. Only an approximation of the true renal fraction can be made since the determinations of renal blood flow and systemic flow were not done simultaneously. In the 4 patients of Group 1 the flow determinations were done on separate days and the renal fraction averaged 34.6 per cent. In the 7 patients of Group 2 in which systemic flow was determined one to two hours prior to renal blood flow measurements the average renal fraction was 34.9 per cent. The range for the 11 subjects studied was from 18.3 to 60.3 per cent and the overall average was 34.8 per cent (Figure 1). The renal fraction in normal subjects as calculated from the standards of Cournand (15) and Smith (12) averages 21.5 per cent. These approximations suggest that in cyanotic patients the relative proportion of the systemic blood flow directed to the kidneys may be increased.

Renal oxygen consumption was measured in 8 patients of Group 2. Excluding the patient J. C. (Number 15 in Table 1) in whom it seems unlikely that the renal vein was accurately catheterized, the observed values ranged from 3.0 to 35.0 cc. per minute and averaged 13.3 cc. per minute. This value is somewhat lower than that calculated for

normal subjects by using renal vein oxygen levels obtained by Warren, Brannon and Merrill (14).[5]

Measurements of urea nitrogen and non-protein nitrogen of whole blood were made in most of the 19 cyanotic patients (Table 1). All levels were essentially normal, showing no evidence of nitrogen retention by the kidneys of these cyanotic individuals.

DISCUSSION

Before any attempt is made to interpret the results of these investigations the differences between the two groups of cyanotic patients studied should be emphasized. In Group 1 the patients were younger, somewhat smaller, and had higher hematocrits than the patients of Group 2. In Group 2 the tests were done in the post-absorptive state, the patients received penicillin[6] and they were subjected to more manipulations as a result of combining the renal studies with cardiac catheterization. The conditions of the Group 2 studies were necessarily more conducive to anxiety.

Despite the variables in the two groups their glomerular filtration rates show very little difference and are essentially normal. The normal filtration rate is maintained in these cyanotic patients despite markedly reduced effective renal plasma flow. Maintenance of the filtration rate

[5] The normal standard for renal oxygen consumption is calculated using the average normal renal arteriovenous oxygen difference of 2.4 volumes per cent (14) and the average normal renal blood flow of 673 cc. per minute per sq. meter in the formula:

$$\text{Renal } O_2 \text{ Consumption (cc./min.)} = \frac{\text{Arterial } O_2 \text{ content (vol. per cent)} - \text{Renal vein } O_2 \text{ content (vol. per cent)}}{100} \times \text{Renal blood flow (cc. per min.)}$$

$$\therefore \text{Renal Oxygen Consumption} = \frac{2.4}{100} \times 673 = 16.2 \text{ cc./min.}$$

The flow of 673 cc./min./sq. meter is obtained by dividing the previously derived normal blood flow (1164 cc./min./1.73 sq. meter) by 1.73.

[6] One patient of Group 1 and 8 patients of Group 2 received 50,000 to 100,000 units of penicillin intramuscularly immediately prior to the clearance studies. The average renal plasma flow in patients receiving penicillin was slightly higher than those who did not receive the drug. Thus, penicillin did not seem to cause any depression of renal plasma flow in this study.

is accompanied by an elevation of the filtration fraction, indicating an increased proportion of water filtered from plasma by the glomeruli.

Smith (8) and others (16) have emphasized the importance of the resistance in the afferent and efferent glomerular arterioles in maintaining the constancy of the glomerular filtration rate and filtration pressure. Smith in particular believes that the tone of the efferent arterioles is of greatest importance in this regard and it is his opinion that low renal plasma flow in the presence of elevation of filtration fraction indicates efferent arteriolar constriction.

In the cyanotic patients of this study the high hematocrits indicate an increase in the viscosity of the blood. The elevated filtration fractions suggest that this high viscosity is increased to an extreme degree in the postglomerular arterioles. An increase in efferent arteriolar or post-glomerular resistance on the basis of increased blood viscosity would appear to be a factor in all of these polycythemic subjects. It is interesting that the patients in Group 1 had higher hematocrits and renal plasma flows than in Group 2 yet the average filtration fraction is higher in the second group. It seems logical to suggest that at least in part these discrepancies are a reflection of efferent arteriolar constriction in Group 2 patients on the basis of apprehension. Psychogenic vasoconstriction has been shown by Smith (8) to produce elevation of the filtration fraction in much the same way as does epinephrine.

The average renal blood flow as calculated by hematocrit in Group 1 was 1997 cc. while in Group 2 it was 1211 cc. The difference in renal blood flows in the two groups is accounted for in part by the depressed plasma flows in Group 2 but the major factor in this difference is the higher hematocrits in Group 1. As would be anticipated from the formula of calculation, the renal blood flow in these patients varies in direct proportion with the hematocrit with few exceptions.

The finding of normal values for Tm and PAH extraction, the absence of nitrogen retention and the normal filtration rates in these cyanotic patients indicate that their kidneys are able to maintain satisfactory excretory function despite the handicaps of chronic anoxemia and polycythemia. This is accomplished in the face of reduced renal plasma flow which probably reflects the greatly reduced proportion of plasma per unit volume of circulating blood as well as some increase in post-glomerular resistance.

The volume of plasma available for clearance in the blood perfusing the kidneys varies in inverse proportion with the red cell volume—the higher the hematocrit, the lower the volume of available plasma. The observed data indicate that the renal blood flow tends to be elevated above the normal standard in the majority of these patients. From a teleological point of view it might be suggested that this is a compensatory mechanism for maintenance of an adequate effective renal plasma flow in these polycythemic patients. The estimates of renal fraction of systemic flow in this group of patients suggest that the elevation of renal blood flow results from an increased proportion of systemic flow directed to the kidneys rather than from an increase in cardiac output.

The data on renal oxygen consumption are too varied to permit a definite conclusion but the overall average suggests a reduction of renal oxygen consumption in these patients. This may reflect the general diminution of oxygen consumption in the cyanotic individual as a whole (2).

It would be of considerable interest to compare the renal hemodynamics of patients with congenital cyanotic heart disease with the findings in polycythemia vera and in chronic high altitude anoxia and polycythemia. In patients subjected to acute anoxia Berger, Gladston and Horwitz (16) found no decrease in renal plasma flow. Alving, et al (17) found no change in renal blood flow, glomerular hemodynamics or filtration rate in 5 normal male adults exposed to simulated altitudes of 10,000 to 18,000 feet for 4 to 6 hours daily over periods of 4 to 6 weeks. The conditions of these experiments, however, are hardly comparable to the chronic anoxia and polycythemia of congenital cyanotic heart disease.

SUMMARY

An investigation of the possible effects of anoxemia and polycythemia on renal hemodynamics was carried out by measurements of PAH and inulin clearances in 19 patients with congenital cyanotic heart disease. In 9 of the patients the clearances were combined with catheterization of the right renal vein. The observed data are presented in tabular form and are compared with previously reported normal standards.

Glomerular filtration rates are found to be normal, but effective

renal plasma flows are depressed and filtration fractions are elevated in these patients. Renal blood flows are above the normal standard in most of the patients and the data suggest an elevation of the renal fraction of systemic blood flow.

It is concluded that the excretory functions of the kidney are maintained in cyanotic subjects despite reduced renal plasma flow. The latter probably reflects the greatly reduced proportion of plasma available per unit volume of circulating blood as well as some increase in post-glomerular resistance.

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BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of this Bulletin)

Haemoglobin. By F. J. W. Roughton and J. C. Kendrew, Editors. XII + 317 pages including an author index. *Interscience Publishers, Inc.*, 1949. $8.50.

This delightful and valuable book is about a great man and a wonderful substance. The subtitle is: *A symposium based on a Conference held at Cambridge in June, 1948, in memory of Sir Joseph Barcroft.*

Thirty-one pages are devoted to the life and work of Sir Joseph Barcroft, told with a pleasing informality by his friends Adrian, Dale, Krogh, Douglass, Hill, Peters, Adair and Roughton. They take the reader behind the "green baize curtain" of the crowded laboratory where "JB" began his experiments and whether there, or on high mountains, or in the decompression chamber, or at congresses, or on the stairs of the laboratory, they succeed in making vivid some glimpses of the man's scientific acumen and integrity, his fine sense of humor, generous nature, courage and perennial enthusiasm.

The scientific papers which were read at the conference comprise the greater part of the book. The editors have classified them in the following sections: Reversible reactions with oxygen and carbon monoxide; Analysis and amino acid composition; X-ray crystallography; Physico-chemical properties; Biochemical and physiological aspects; Differences between adult and foetal haemoglobin; Comparative biochemistry and physiology of oxygen carriers. This reviewer refrains from listing the titles of the several papers in each of the sections believing that anyone with any interest in haemoglobin will do well to seek, himself, the summaries of achievements up to June, 1948, in the words of investigators each of whom is an authority in his sector.

An exception is made by citing an article that one would not expect to find in a book entitled *Haemoglobin.* This is an introduction to fascinating papers on the molecular architecture of haemoglobin and myoglobin in which introduction Kendrew and Perutz describe in relatively simple terms the application of X-ray crystallographic techniques to the study of large molecules. It is the clearest elementary treatment of an inherently complicated subject that the reviewer has seen. One cannot refrain from adding Perutz's remarks that a detailed analysis of the X-ray data on a molecule of moderate size, such as that of cholesterol, takes two or more man-years to complete and that the success achieved with the relatively huge molecule of haemoglobin was due in large measure to uniquely favorable features of the crystal. Thus, to the long list of properties which make haemoglobin the outstanding example of well nigh perfect adaptation of molecular forces to physiological functions one might add adaptation of molecular architecture to the

requirements of the crystallographer who seeks a glimpse of architectural features common to all globular proteins.

To compress 28 papers into 276 pages has required condensation of much that has been published in detail. This is to the advantage of the reader who seeks the perspective that otherwise could be acquired only by studying a voluminous literature. The reader also will find lists of selected references. In several instances the summarizations are models of clarity. Each paper is by an active investigator well qualified to state the particular problem, to summarize the principal data, to indicate restrictions on interpretations, and to expose doubtful matters requiring further clarification.

L. J. Henderson is reported to have said of Barcroft's *The Respiratory Functions of the Blood* that it revealed "enough unsolved problems to last twenty years." Now, more than twenty years since the publication of the parts of Barcroft's fascinating book, one who reads the *Haemoglobin* of 1949 will see that, while a great deal is known, much still remains to be done. The reader also will note the indications that henceforth investigations of the properties and functions of haemoglobin are likely to be so refined that he who hopes to follow developments had best get his bearings from this book.

Nor should one miss the book's flavor, remindful of Barcroft. It stimulates hunger for more of this rich food.

WM. MANSFIELD CLARK

A Textbook of Physiology (originally by WILLIAM H. HOWELL, M.D.). Edited by JOHN F. FULTON, M.D. *W. B. Saunders Co.*, 1949. 1258 + xi pp.

This is the 16th edition of this famous text and the second revision by the present editor. It is a series of monographs written, for the most part, by the editor and his colleagues at the Yale University School of Medicine, each of whom has had extensive experience in the field which he describes. The text is embellished with 553 figures and 70 tables. The majority of these illustrations are helpful; a few are so complicated that their presentation here, ripped from the original paper, may prove confusing to the uninitiated reader. There are bibliographies at the end of each chapter which are good generally, but in some chapters references are furnished which deal only with one view on a moot point. The format and typography set a standard of extraordinary excellence rarely equalled in modern texts.

The degree of emphasis placed on the several special fields in physiology warrants some comment because it is unusual. There are 1200 odd pages of text divided as follows: peripheral and central neurophysiology *41* p.c.; circulation *18* p.c.; endocrines *10* p.c.; blood, body fluids and renal function *9* p.c.; gastrointestinal *8* p.c.; metaboiism and nutrition *8* p.c.; respiration *6* p.c. It would be unwise to judge the balance in distribution of emphasis solely by the number of pages devoted to the various sections, but in this case the correlation is high. It may be questioned whether a textbook of physiology, designed presumably as a source of basic reading for students of biology and medicine, fulfills its obligations by disproportionate emphases such as the following: 16 pages cover the vast field of gas exchange and

transportation and 18 pages are devoted to the organization of neural mechanisms responsible for rhythmic respiration; 16 pages present the field of renal physiology and 72 pages are assigned to various aspects of vision; 11 pages for the thyroid and 13 pages for the cytoarchitecture and projections of the cerebral cortex. The relations listed above underline the unevenness of the essays which compose this text. Some chapters are extensive and detailed monographs, others are cursory outlines by comparison. And the emphasis placed on various fields reflects, quite naturally, the particular interests of the Department of Physiology at New Haven. It should be stressed strongly that the great value of this textbook is the competent and extensive presentations by experts in several special fields. For example, and there are many others, Lamport's essay on hemodynamics presents in one site a discussion of principles unique in its scope; and Nahum and Chernoff's skillful treatment of the electrocardiogram requires over 40 pages (more than 3 p.c. of the whole text) to present newer aspects of this field; Lloyd's presentation of the basis of electrical excitability is invaluable. These and many others are valuable monographs but their extensiveness appears somewhat disproportionate in a textbook of this sort.

For the reasons set forth this reviewer is grateful to the editor and authors for making available many invaluable monographs but believes that as a well-rounded source for general reading this present edition could not be recommended as the *only* text for the beginning student of physiology.

The concluding paragraph in the introductory chapter deals with an anxiety current in the minds of some physiologists: the necessity for preserving physiology as "an academic discipline in its own right" and the belief that "its future will be determined by the extent to which it remains a pure, rather than an applied, science". The sense of these remarks depends upon the connotation of the words "applied" and "academic." There can be little doubt that few significant advances will be made, for example, by physiologists who are employed to measure the effects of tobacco smoke on the rabbit's conjunctiva. In this sense applied physiology is not fruitful. But how does one assess the fundamental contributions pouring from laboratories during the war in response to specific military needs: many by necessity were pedestrian, others illuminated many basic processes and mechanisms. The future of physiology is secure as long as physiologists ask serious questions of nature, perform precise experiments, observe alertly, record accurately, analyse discriminatingly and speculate imaginatively. It will make little difference whether this be done in university, government or industrial laboratory as long as it is done. If the work is true it is pure.

J. L. L., Jr.

The Eye and Its Diseases. By Conrad Berens. *W. B. Saunders and Company,* 1949, Second Edition, 1092 pages.

This is the second edition of the textbook edited by Doctor Berens. It is divided into thirteen sections and seventy-six individual chapters, some chapters being by several authors. There are ninety-two contributors to this volume.

The format of the book has been considerably improved. Practically the entire text has been rewritten and brought up to date. The illustrations are clear-cut and excellent.

The book suffers from the same failing which is inherent to all books which are the products of different contributors. Many of the chapters are excellent and are really notable contributions. Others are usual run-of-the-mine articles, while still some few chapters are completely inadequate. Thus, the important subject of ocular tuberculosis is dismissed with a brief five pages and the subject of ocular syphilis is covered in three pages. Attached to many of the chapters are bibliographies. In some cases these are thoroughly complete giving all the important literature, while in other cases the bibliography given apparently represents only the literature used to assemble the material. Still other chapters have no bibliographies whatsoever. However, despite the unevenness of the volume, taken all in all, it is a thoroughly worthwhile textbook for the specialist. Even though some phases of ophthalmology are poorly covered under their respective titles, they are nevertheless adequately covered under other sections of the book by other authors and a thoroughly good index makes the material readily accessible.

A. C. W.

Radiologic Exploration of the Bronchus. By S. Di Rienzo. 332 pp. $10.75. *Charles C. Thomas, Springfield, Illinois.*

Dr. Di Rienzo's book is one of the most important contributions on this subject to date. It contains a comprehensive presentation of the embryology, anatomy, physiology and pathology involved in radiologic studies of the lungs. There is an excellent bibliography; the typography is clear and the plates beautifully reproduced. Anyone interested in lung disease will find this an extremely rewarding volume.

A small part of the book deals with ordinary radiographic studies and the tomogram. The remainder is devoted to the bronchogram. The major difference between the technique described for bronchography and that usually practiced elsewhere lies in two factors. First, the radiographs themselves show the outline of the tracheobronchial tree with a clarity (in the experience of this reviewer) not duplicated by other workers in the field. The quality of the films testifies to the extreme care which must have been exercised in each individual case. Second, the value of serial studies (observations during the instillation of the oil), correlation of appearances at different times with the position of the patient, the stage of respiration, etc. is demonstrated again and again.

Considerable importance is attached to "bronchial dynamism and tone" which are "expressed by variations in the calibre of the bronchi, by peristaltic waves, and by the action of the branch sphincters." The excellent illustrations leave no doubt in the reader's mind of the existence of these phenomena, and the patients cited show clearly their importance. The difference between lung anatomy as studied in the cadaver and the functional anatomy as seen in the patient is stressed throughout.

The section on the "physiopathology of the cough" analyzes this important function with great care. The author concludes that: "In the bronchus it is not the air that expulses the secretions during the act of coughing; the air itself is expulsed by the bronchus by a peristaltic expulsive wave. . . ." The accompanying illustrations again do much to persuade the reader of the validity of this statement.

His suggestion that bronchoscopy should be carried out after bronchography is not in keeping with the views of most workers in this field. He also states that—"bronchography is contraindicated in a case of active tuberculosis." This view is no longer held in this country. Some of the theory in regard to the pathogenesis of of bronchiectasis is open to question and not adequately developed.

D. F. P.

Fundamentals of Otolaryngology. By LAWRENCE R. BOIES. 443 pp. $6.50. *W. B. Saunders Co., Philadelphia, Pa.*

Dr. Boies' textbook (prepared with the assistance of several of his associates) is intended for the use of the medical student and the medical practitioner who is not an otolaryngologist.

As such it is an excellent presentation, not only of generally sound clinical information, but the anatomy and physiology related to diseases of the ears, nose and throat.

It is very well illustrated and the bibliography is extensive and well selected.

D. F. P.

Clinical Neurology. By BERNARD J. ALPERS. *F. A. Davis Company, Phila. 3, Pa.* 862 pp. $9.50.

The second edition of this textbook of clinical neurology, if read critically, is an addition to the standard teaching literature on the subject. It contains some good clinical descriptions which reveal the experience of the author. It is well put together, well published, and contains reasonable illustrations.

To the reviewer, however, this clinical presentation is marred to some extent by the interjection of experimental digressions which are sometimes inappropriate or unsubstantiated. Abnormal muscle contractions under different conditions receive such treatment, for example, as do certain comments on peripheral nerve function. One would prefer to see a less wide-spread recommendation of proprietary agents by name. This is especially true when, as in the case of sodium phenyl hydantoinate, several different trade names are used without explanation, or of "nirvanol" which is not without danger. The liberal use of tables tends to imply an assumption of distinction or validity in their contents which is not always warranted. For didactic teaching this may be justified to some extent, but the emphasis on routine test procedures rather than a considered functional assessment finds less justification. The frequent use of the words "neuritis," "cerebral vascular spasm," etc., raises doubts in the mind of the reader. There are several more detailed criticisms—the use of the Swift Ellis treatment—inaccuracy in description of cervical root distributions—the statement that aneurysms usually warrant

exploration—the differentiation of optic neuritis and choked disc—the statement that cord tumour may be distinguished from polyneuritis by the protein elevation in the former—and so on. There are others.

Nevertheless, while this book cannot be recommended to the uncritical reader, its general level is high. More important, in these times, it is a good clinical descriptive book by an able clinician.

J. W. M.

Diagnosis and Treatment of Brain Tumors and Care of the Neurosurgical Patient. ERNEST SACHS. *St. Louis, C. V. Mosby Co.*, 1949, 552 pp., price $15.00.

This book is a combined second edition of two monographs which the author published originally under the titles of "The Diagnosis and Treatment of Brain Tumors" and "The Care of Neurosurgical Patients Before, During and After Operation." These two books have been integrated without making the resultant volume unwieldy. There does not seem to be much change in the format or material of the book. The viewpoint, that of a progressive pioneer in neurosurgery, is clearly presented and fundamentally sound. Based upon his wide experience, the author's discussion of brain tumors is authoritative and accurate. However some of the surgical techniques are not so applicable now as they were when the book was first written in 1931. One might cite as an example the treatment of brain abscess. The writer admits that the entire problem of brain abscesses has been changed in the last decade, but his discussion of the subject deals with the prepenicillin management. Although very brief mention has been made of the newer diagnostic techniques, angiography and electroencephalography, their discussion is quite inadequate considering the value placed upon these procedures at the present time.

The numerous illustrations are particularly good and there is a good index.

The book is recommended as a reference volume for students and as essential reading for all post-graduate students interested in the field of neurology.

A. E. W.

Advances in Surgery. Vol. I. Editorial Direction, WILLIAM DEWITT ANDRUS, M.D. 554 pp. $11.00. *Interscience Publishers, Inc., New York.*

This is the first volume of a proposed series of publications devoted to recent advances in surgery and "developments in other fields which may contribute to surgical therapy."

The seven articles which are assembled in this initial volume have obviously been selected by the editors on the basis of the authors' contribution to the subject under discussion. Each topic is given a full 40 to 100 page coverage with an extensive bibliography and an adequate number of illustrations.

To be particularly recommended is the excellent discussion of traumatic shock by Dr. Jacob Fine in which investigative work of the last decade from many laboratories is presented, critically evaluated and supplemented by contributions from the author's own investigations.

Cole, Reynolds and Ireneus give a summary of their extensive experience with

strictures of the common duct. The use of antibiotics in surgery is reviewed by Rhoads and Zintel. Blakemore and Lord discuss blood vessel anastomosis by means of the non-suture vitallium tube method, a technique which at the present time even the authors are apparently tending to abandon in favor of suture anastomosis. Immersion foot syndrome is dealt with by C. C. Ungley, an English surgeon whose experience with this difficult problem in the last war was a considerable one. J. Z. Young of the Department of Anatomy, University College, London presents a thorough study of factors influencing the regeneration of nerves. Coley and Higinbotham discuss tumors of bone in a well organized presentation which contains 60 or more excellent photographs and reproductions of roentgenograms.

This book is to be recommended to students and surgeons as a reference work in its seven specific subjects.

H. W. S., Jr.

An Atlas of Amputations. By Donald B. Slocum, M.D., M.S. *Published by The C. V. Mosby Company.*

This work is more than the name implies. It is an extensive text and treatise on amputations, in addition to being an atlas. It is a large book, well-planned, with easily readable type.

It takes up the question of amputations from the point of view of indications, precautions, surgical techniques, variations in types, conditioning of the stumps, the prosthetics and the fitting of prosthetics and the training and rehabilitation of amputees. It is particularly valuable because it carries through an entire program of the amputation problem. I know of no other single source which is so complete as this new volume.

The sections on anesthesia and physical medicine are particularly good. The work is amply illustrated, most of the illustrations coming from Army sources—Walter Reed Hospital in particular. The illustrative diagrams are exceptionally clear and well done. The posture work and muscle testing parallels very closely the work of Kendall here in Baltimore.

The question of amputations in tuberculosis does not mention the use of streptomycin which we have found may at least postpone the former dictum of amputation in a tarsal tuberculosis.

This volume is a very valuable reference work for the surgeon who is doing amputation surgery.

E. J. McD.

Nervous and Neurohumeral Regulation of Intestinal Motility. By W. B. Youmans. 129 pp. $4.75. *Interscience Publishers, Inc., New York.*

This monograph is a summary of the present status of knowledge concerning regulation of the motility of the small intestine. Dr. Youmans has been interested in this phase of physiology for the last 15 years and his own careful observations make up the bulk of the monograph. Numerous experimental techniques and recording methods for physiologic and pharmacologic studies of intestinal activity

are described in detail. Experimental evidence is presented clearly and critically. A detailed summary at the end of each chapter aids the reader greatly in the interpretation of the data. This work will be of greatest value to those who pursue investigations in this rather specialized field.

H. W. S., Jr.

The Diagnosis and Treatment of Adrenal Insufficiency. By George W. Thorn. American Lecture Series, Publication Number 29. *Charles C. Thomas, Springfield, Illinois,* 1949.

A short, concise monograph, written with clarity and well documented by diagrams and specific case histories to illustrate certain points. Diagnostic tests and criteria are outlined in simple language; and therapeutic programs are given to meet variations in severity and complicating factors. The author's large experience with experimental and clinical adrenal insufficiency, together with his lucid style, makes this booklet worthwhile and entertaining reading for both the practitioner and the expert in the field.

J. E. H.

BOOKS RECEIVED FOR REVIEW

An Atlas of Amputations. By DONALD B. SLOCUM. 562 pp. $20.00. *C. V. Mosby Co. St. Louis, Missouri.*

Acute Appendicitis and Its Complications. By FREDERICK FITZHERBERT BOYCE. 487 pp. $8.75. *Oxford University Press. N. Y.*

Advances in Internal Medicine, vol. 3. Edited by WILLIAM DOCK and I. SNAPPER. 478 pp. $8.50. *Interscience Publishers, N. Y.*

Advances in Pediatrics, vol. IV. Edited by S. Z. LEVINE and others. 316 pp. $6.50. *Interscience Publishers, N. Y.*

Antibiotics. Edited by GEORGE W. IRVING, JR. and HORACE T. HERRICK. 273 pp. $6.75. *Chemical Publishing Co., Inc., Brooklyn, N. Y.*

Applied Biophysics. Edited by N. HOWARD-JONES. 293 pp. $6.75. *Chemical Publishing Co., Inc., Brooklyn, N. Y.*

Blakiston's New Gould Medical Dictionary. Textbook Edition. By HAROLD JONES, NORMAND HOERR and ARTHUR OSOL. 1294 pp. $8.50. *The Blakiston Co., Phila. 5, Pa.*

Clinical Diagnosis by Laboratory Examinations, 2nd edition. By JOHN A. KOLMER. pp. 1212, $12.00. *Appleton-Century-Crofts, Inc., N. Y.*

Clinical Interpretation of Laboratory Tests. By RAYMOND H. GOODALE. 622 pp. $6.50. *F. A. Davis Co., Phila. 3, Pa.*

Clinical Neurology. By BERNARD J. ALPERS. 862 pp. $9.50. *F. A. Davis Co., Phila. 3, Pa.*

Diagnosis and Treatment of Brain Tumors and Care of the Neurosurgical Patient, 2nd edition. By ERNEST SACHS. 552 pp. $15.00. *C. V. Mosby Co., St. Louis, Missouri.*

Digitalis and Other Cardiotonic Drugs revised, enlarged 2nd edition. By ELI RODIN MOVITT. 245 pp. $5.75. *Oxford University Press, N. Y.* 11.

Diseases of the Heart. By CHARLES K. FRIEDBERG. 1081 pp. $11.50. *W. B. Saunders, Phila., Pa.*

Fractures, 5th edition. By PAUL B. MAGNUSON and JAMES K. STACK. 537 pp. $7.00. *J. B. Lippincott Co., Phila., Pa.*

Functional Localization in Relation to Frontal Lobotomy. By JOHN F. FULTON. 140 pp. $3.00. *Oxford University Press, N. Y.* 11.

Hematin Compounds and Bile Pigments. By R. LEMBERG and J. W. LEGGE. 748 pp. $15.00. *Interscience Publishers, Inc., N. Y.* 3.

Multi-Enzyme Systems. By MALCOLM DIXON. 100 pp. $1.75. *Cambridge University* Press, N. Y.

Minutes of the Seventh Streptomycin Conference, held at Denver, Colorado. 360 pp. Veterans Administration.

Physiology of the Uterus, 2nd edition. By S. R. M. REYNOLDS. 611 pp. $12.50. *Paul B. Hoeber, Inc., N. Y. 16.*

Streptomycin, Its Nature and Practical Application. Edited by SELMAN A. WAKSMAN. 618 pp. $10.00. *The Williams and Wilkins Co., Baltimore, Md.*

Surgical and Maxillofacial Prosthesis. By OSCAR E. BEDER. 51 pp. $3.00 *King's Crown Press, Columbia University, N. Y. 27.*

Textbook of Physiology. 16th edition. By JOHN F. FULTON. 1258 pp. $10.00. *W. B. Saunders Co., Phila., Pa.*

Textbook of Surgery, 5th edition. By FREDERICK CHRISTOPHER. 1550 pp. $13.00. *W. B. Saunders Co., Phila., Pa.*

The Cry and the Covenant. By MORTON THOMPSON. 469 pp. $3.50. *Doubleday & Co., Inc., N. Y. 20.*

The Diagnosis and Treatment of Adrenal Insufficiency. By GEORGE W. THORN. 171 pp. $5.50. *Charles C. Thomas, Publisher, Springfield, Illinois.*

The Eye and Its Diseases, new 2nd edition. Edited by CONRAD BERENS. 1092 pp. $16.00. *W. B. Saunders Co., Phila., Pa.*